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(JULY 2022 – JUNE 2025)

TITLE

STUDY OF THE LONG TERM OUTCOMES OF HIGH GRADE GLIOMAS, THEIR CORRELATION WITH IMMUNOHISTOCHEMICAL MARKERS AND THE CLINICAL EVOLUTION OF ISOCITRATE DEHYDROGENASE POSITIVE TUMORS

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COVERING LETTER

To,

The Chairperson,

IHEC-PGR, AIIMS Bhopal

Subject: Submission of Thesis Protocol

Respected sir,

I, Dr. Abhishek Latish Shetty, have joined the Department of Neurosurgery at AIIMS Bhopal as Mch Senior Resident in July 2022 session. I am hereby submitting my Thesis titled **"STUDY OF THE LONG TERM OUTCOMES OF HIGH GRADE GLIOMAS, THEIR CORRELATION WITH IMMUNOHISTOCHEMICAL MARKERS AND THE CLINICAL EVOLUTION OF ISOCITRATE DEHYDROGENASE POSITIVE TUMORS"** for your kind approval.

Thanking you.

Yours sincerely,

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I, **Dr Abhishek Latish Shetty**, Mch senior resident registered in batch July 2022, hereby declare that the data submitted for my Mch thesis belongs to me and is original. I also certify that the work was done by me to carry out this study.

This institute shall not be responsible for any dispute or any conflict of interest that may arise out of this thesis at any stage.

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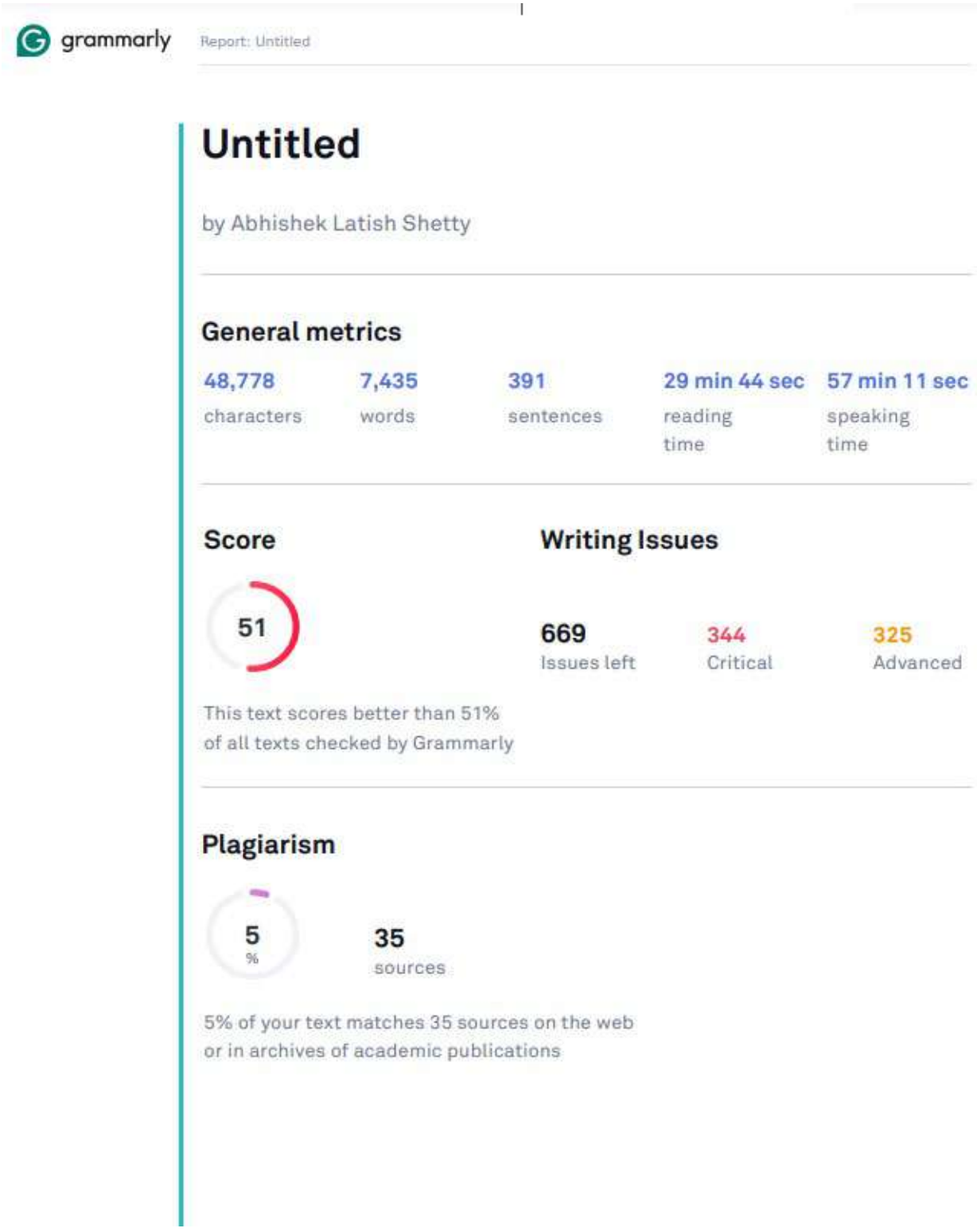

IHEC Permission Letter

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Saket Nagar, Bhopal – 462020 (M.P)
Institutional **Human Ethics Committee- Student Research (IHEC-SR)**
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Ref Number: AIIMS BPL/IHECSR/July/22/SS/06 **Date:** 28th February 2023

Letter of Permission

Student Investigator: Dr. **Abhishek Latish Shetty** Neurosurgery	**Guide:** **Dr. Adesh Shrivastava** **Neurosurgery** **Co-Guides:** **Dr Sumit Raj, Dr Amit Agrawal**

AIIMS, Bhopal Institutional Human Ethics Committee- Student Research (IHEC-SR) in its 7th meeting held on 22nd February 2023 discussed your proposal titled **"Study of the long term outcomes of high grade gliomas, their correlation with immunohistochemical markers and the clinical evolution of isocitrate dehydrogenase positive tumors"** and evaluated it for suitability for your dissertation as required for fulfilment of DM/M.Ch program.

Following members attended the meeting:

1. Prof. D. K. Pal, Former HoD Community Medicine, GMC, Bhopal.....Chairperson
2. Prof. Rajnish Joshi, Professor of General Medicine, AIIMS, Bhopal.....Member
3. Prof. Amit Agrawal, Professor of Neurosurgery, AIIMS, Bhopal.....Member
4. Dr. Sunita Athawale, Professor of Anatomy, AIIMS, Bhopal.....Member
5. Dr. Girish Bhatt, Addl. Professor of Paediatrics, AIIMS, Bhopal.....Member
6. Dr. Ujjawal Khurana, Assoc. Professor of Pathology, AIIMS, Bhopal.....Member
7. Dr. Ankur Joshi, Assoc. Professor of CFM, AIIMS, Bhopal.....Member
8. Mr. Trivesh Goswami, Law Officer, AIIMS Bhopal.....Member
9. Dr. Shashank Purwar, Professor of Microbiology, AIIMS, Bhopal.....Member Secretary

The decision of the committee is as follows:

The AIIMS, Bhopal IHEC-SR approves your research protocol. All research related activities must begin only after the date of this approval. The validity of this approval is till two years from the date of issuance. Please submit a closure report / renewal request before expiration of the validity for this approval.

Shashank Purwar

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Dr. Abhishek Latish Shetty

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Appendix 2: List of abbreviations

IDH: Isocitrate dehydrogenase

ATRX: alpha thalassemia retardation/ x linked

Olig 2: Oligodendrocyte transcription factor 2

GFAP: Glial fibrillary acidic protein

KPS: Karnofsky performance score

ECOG: Eastern cooperative oncology group

HGG: High grae glioma

LGG: Low grae glioma

IHC: Immunohistochemistry

INTRODUCTION

It is important to understand the burden of CNS tumors in India. The incidence of CNS tumors in India ranges from 5-10 per 100000 population and accounts for 2% of all malignancies.40,000-50,000 people are diagnosed with CNS tumor every year and this number is on an increasing trend. The median age of glial tumors was seen to be at least a decade earlier than that reported in the Western population. The most common primary central nervous system tumors are gliomas. They originate from the glial cells. Gliomas are graded based on histopathological analysis of tumor differentiation, mitotic activity, nuclear atypia, cellularity and the extent of microvascular proliferation. As this led to a great deal of interobserver variability, quantitative molecular analysis was adapted for the staging of gliomas hence improving prognostication and management plans. Gliomas range from Grade 1 to 4 with grade 1and 2 being classified as low grade glioma and grade 3and 4 as high grade glioma. Since 2016, gliomas have been classified based on not only their histopathological appearance but also on molecular parameters. Mutations in Isocitrate dehydrogenase 1/2 are an important feature of WHO grade 2 and WHO grade 3 glial cell tumors and have significantly better prognosis than the non mutant or IDH wild type variant. Hence IDH wild type Grade 2 gliomas are also considered as high grade glioma.The aims of this study are to assess the demographic profile of glioma patients presenting to our center, to evaluate the long term outcomes of high grade glioma, its correlation with immunohistochemical markers and to study the clinical evolution of IDH positive tumors.

Classification and nomenclature:

The classification and grading of gliomas has been evolving over time. The earliest classification was given by Bailey and Cushing in 1926 and was later revised by Kernohan,Ringertz and others.Presently the classification of gliomas is based on the WHO classification of Central Nervous System Tumors which was first published in 1979 and has been revised five times since then most recently in 2021.The incorporation of molecular parameters into the classification was done in 2016.In 2021 the WHO introduced major changes that advanced the role of molecular diagnostics in CNS tumor classification at the same time keeping into account the other established approaches to diagnosis such as histology and immunohistochemistry. Hence it recommended a 4 layered reporting structure for CNS tumors which included

1.Integrated diagnosis

2.Histologic diagnosis

3.CNS WHO Grade

4.Molecular information[1]

Incidence

Gliomas account for 80% of primary malignant brain tumors.[2] Brain tumor incidence rates have increased over the past three decades, with improved reporting, increased use of diagnostic imaging, and changing attitudes toward diagnosis in the elderly all suspected to account for much of this observed increase.[3] Incidence rates for all primary brain and other CNS tumors combined were higher among females (25.31 per 100,000 population) than males (20.59 per 100.000 population) though the incidence for neuroglial tumors was more in males than females.[4] Diffusely infiltrating astrocytomas encompass nearly 75% of all astrocytic tumors. This group can be further subclassified as

a. Diffuse Astrocytoma (WHO Grade 2) makes up 10-15% of all astrocytic tumors

b. Anaplastic astrocytoma (WHO Grade 3)

c. Glioblastoma multiforme (WHO Grade 4) which accounts for more than 60% of all astrocytic tumors and more than 45% of all primary intracranial tumors making it the most common primary intracranial neoplasm in adults.[5]

Generally, within histologic types, the survival time decreases with age. The mechanisms for the strong, consistent inverse association between age and survival are poorly understood. In the case of glioma, this association is at least partially attributable to the frequency with which prognostically relevant somatic mutations are observed in patients of different ages. The most relevant of these mutations is probably that of isocitrate dehydrogenase type 1 (IDH 1) associated with younger disease onset but improved overall survival.[6]

Most malignant brain tumors are high-grade gliomas, and most of these are GBM, a WHO grade IV tumor The remainder are WHO grade Ill tumors such as anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma. Men are more commonly affected than women. The peak incidence of occurrence of these tumors is the age of 65 years to 75 years, and the median survival time is inversely proportional to age. All grade 2 IDH wild type gliomas also behave clinically like high grade tumors.

Prognosis

The following variables are robustly associated with better glioblastoma prognosis: younger age, IDH mutation in the tumor, higher Karnofsky Performance Scale score, greater extent of resection and capacity for complete resection, lower degree of tumor necrosis, less contrast enhancement in the tumor on preoperative magnetic resonance imaging studies, decreased volume of residual disease, smaller preoperative and postoperative tumor size, and more

favorable tumor location (poorer survival is associated with tumor infiltration of the splenium, basal ganglia, thalamus, or midbrain).[7,8] Patients with high grade gliomas have a mean survival time of just 4-6 weeks with symptomatic care and just 12-18 months with maximal tumor resection and appropriate adjuvant therapy Currently, the standard of care for high-grade gliomas involves three components: maximal surgical resection followed by external beam radiation therapy and chemotherapy with temozolamide or other alkylating agents though addition of temozolomide has improved median survival time only by approximately 2.5 months.[9]

REVIEW OF LITERATURE

In 1918, Pervical Bailey who had completed his medical internship started pursuing his interest on the workings of the brain and joined Cushing in his endeavour who had been amassing an extensive repository of brain tumor specimens. It was understood by then that some brain tumors were aggressive whereas others were benign. Bailey examined more than 400 of Cushing's specimens correlating microscopic appearance with clinical outcomes.[10] The resulting publication of Bailey and Cushing demonstrated that the cellular structure of tumors can guide treatment and prognosis.

Gliomas are tumors from the glial cells of the brain and spinal cord and are the most common primary intracranial tumors found in adults.[11] They are subclassified based on the cell of origin (astrocytes/oligodendrocytes/ependymal cells). Gliomas have a broad spectrum of biologic aggressiveness.

Outcome prediction in glioma is essential as it has the potential to aid in optimal patient management and patient counselling. In the past, outcome prediction has centred mainly on clinical features such as age and performance status, surgical features such as resection status, and pathological features such as morphology and Word Health (WHO) grade.[12] Molecular classification and identification of predictive and prognostic factors are now also considered.

NADP+ dependent isocitrate dehydrogenases IDH1 and IDH2 catalyze the conversion of isocitrate to alpha-ketoglutarate through oxidative decarboxylation which reduces NADP to NADPH.They have different subcellular localizations. IDH1 is present in cytoplasm and perioxisome and IDH2 resides in mitochondria.[13]

One of the most important landmark studies in glioma research was done by Hai Yan et al. In his study, mutations were identified affecting amino acid 132 of IDH1. This was present in more than 70% of WHO grade II and III astrocytomas and oligodendrogliomas. Glioblastomas that developed from these lower-grade lesions also had these mutations. Tumors without mutations in the R132 aminoacid of IDH1 often had mutations affecting the amino acid (R172) of the IDH2

gene. Tumors with IDHI or IDH2 mutations had distinctive genetic and clinical characteristics, and patients with such tumors had a better outcome than those with wild-type IDH genes. Each of four tested IDHI and IDH2 mutations reduced the enzymatic activity of the encoded protein.[14]

Sumihito Nobusawa et al studied the frequency of IDHI mutations in glioblastomas at a population level and assessed whether they can discriminate between primary glioblastomas and secondary glioblastomas that progressed from low-grade or anaplastic astrocytoma. IDHI mutations were detected in 8.8%. Glioblastoma patients with IDH1 mutations were younger (mean, 47.9 years) but those patients who had EGFR amplification (60.9 years) had significantly longer survival (mean, 27.1 versus 11.3 months; $P < 0.0001$). IDH I mutations were frequent in glioblastomas diagnosed as secondary (22 of 30; 73%), but rare in primary glioblastomas (14 of 377; 3.7%: $P< 0.0001$).[15]

The IDH gene product that normally converts isocitrate into alpha-ketoglutarate, when mutated, result in enzyme products that instead drive conversion of isocitrate into 2-hydroxyglutarate (2HG) which competitively inhibits downstream histone demethylases contributing to abnormal regulation of gene expression in these cancers.

In the study performed by Jalal Ali Jalal et al it was found that ATRX is frequently expressed in grade Il and III astrocytomas and was significantly related to the patient's age, tumor location, tumor type and grade, so it can be a good diagnostic and prognostic indicator for glioma.[16]

Dahuja Get al did a prospective study that included 115 glioma patients. IHC markers (isocitrate dehydrogenase [IDH] ,1 ATRX, P53, Ki-67 antibody) were done in all patients. Patients received treatment as per the grade of tumor. The patients were followed in 3 monthly intervals, for a period of 12 months. There were 1 Grade ,1 3 Grade 2, 26 Grade 3 and 54 glioblastoma multiforme (GBM) patients out of which 10 patients were secondary GBM cases. IDHI mutation is frequent in Grade 2 and Grade 3 of both astrocytic and oligodendroglia tumors. IDH1 mutation is also common in secondary GBM patients. It was concluded from the study that the molecular nature of diffuse astrocytoma and anaplastic astrocytoma cases can be confirmed accurately by combined IDH1 and ATRX IHC.[17]

Kurtkaya-Yapicier O et al studied that p53 immunoreactivity in astrocytes could be useful in differentiating benign reactive lesions from malignant astrocytomas. In their study, an immunohistochemical analysis on 110 brain lesions from 108 patients using a monoclonal antibody (DO-7) against p53 protein was conducted. Using the modified Ringertz and World Health Organization system, the specimens included 22 astrocytomas, 12 anaplastic astrocytomas, 42 glioblastoma multiforme tumors, three non glial tumors, and 56 reactive astrocytic lesions to 25 neoplasms, nine infectious processes, 6 cerebrovascular disorders, 1 metabolic disorder, 2 vascular malformations, 11 degenerative/ demyelinating lesions, and 2 unknown primary lesions. Immunoreactive astrocytic tumors included 54 % astrocytomas ,75% anaplastic astrocytomas, and 38 glioblastoma multiforme tumors (90%). Among the reactive astrocytic lesions, only 5(9%) cases of progressive multifocal leukoencephalopathy (PML) were immunoreactive. These data demonstrate that p53 immunoreactivity in astrogliosis is unusual but is to be expected in astrocytomas and can help to differentiate reactive from neoplastic astrocytic lesions.[18]

Napieralska A et al performed a multi institutional Polish study on the long term outcomes of high grade gliomas. The study group consisted of 28 patient all of whom underwent surgery as the primary treatment. Chemotherapy was given in 93% of children with about one third of them being treated with temozolomide. After or during treatment, 79%of them received radiation therapy with a median dose of 54 Gy. Median follow-up was 122 months, and during this period, 59 patients died. The 1-, 2-,5-and 10- year overall survival (OS) was 78%,48%,%30 and 17%, respectively. Patients with radical resection and temozolomide-based chemotherapy had better OS. Progression-free survival was better in patients after radical resection and radiotherapy. The best outcome in high grade glioma patients was observed after R0 resection with immediate postoperative temozolomide-based chemotherapy and radical radiotherapy.[19] The biggest drawback of this study is that it included only pediatric Polish patients hence its results cannot be extrapolated to the general population.

A systematic review of literature on this subject was done by Khan I et al. In this review they evaluated the prognostic significance of IDH1 mutation based on published evidence. Multiple retrospective clinical analyses correlate the presence of IDH1 mutation in GBM. These patients have good prognostic outcomes compared to wild-type IDH1. The systematic review reported

similar results. IDH1 mutation is an independent factor for longer overall survival (OS) and progression free survival in patients with GBM patients when compared to wild-type IDH1.[20]

Chromosome 1p/19q codeletion and IDH mutation were the molecular markers which in additional to histology provided improvements in the diagnostic and prognostic stratification of lower grade gliomas represented the cornerstone of the 2016 WHO classification of tumors of the Central Nervous System.[21]

There are three types of gliomas which are based on their phenotypic cell characteristics: astrocytomas, oligodendrogliomas and ependymomas.

Atrocytomas originate from astrocytes and can be encapsulated or infiltrative. Lower grade tumors are found in children and higher grade in adults. Oligodendrogliomas arise from oligodendrocytes. They are less infiltrating than astrocytomas. The lining the ventricles and the central canal of the spinal cord are ependymal cells which are the origin of ependymomas. According to the 2021 recommendations for CNS tumors, astrocytomas are now diagnosed solely by IDH mutations. Oligodendrogliomas by definition have 1p/19q codeletions with IDH mutations.[22]

The prognostic and predictive value of IDH mutations were confirmed by the results of the EORTC,RTOG an NOA trials. Besides molecular profile, other factors like KPS,size of tumor, age, extent of resection and the presence of neurological deficits before surgery all provided prognostic information.[23]

The most commonly used method for assessing IDH mutation status is immunohistochemical analysis obtained after biopsy or surgical resection. Upto 15% of IDH mutated gliomas are not detected by traditional IDH1 (p.R132H) antibody testing.[24]

ATRX gene plays an important role in chromatin remodeling, histone deposition, cell cycle regulation and genomic stability. Deciphering a comprehensive role for ATRX in gliomas is still in its infancy. There is a strong association between IH mutations and ATRX mutations but cooccurrence of 1p/19q codeletion and ATRX loss have been nearly non existent.This helps determine whether a tumor is of astrocytic or oligodendritic lineage without requiring both studies.[25]

Ikemura and colleagues documented that ATRX loss glioblastomas in younger patients were due to tumors most commonly non hemispheric in location.[26]Ebrahimi and colleagues found these patients to have H3F3AG34 or K27 mutations.[27]

Other studies also show that in IDH mutated tumors, ATRX retention is not mutually exclusive of 1p/q19 codeletion. Hence it is recommended that both IDH status and ATRX status be assessed in all gliomas.[28] Furthermore, sequencing of IDH1/2 and H3F3A genes should be done in all ATRX loss gliomas.

Liu and colleagues observed loss of ATRX expression within secondary glioblastomas and more in younger population.[29] Whereas Cai and colleagues observed lower ATRX expression more prominently in primary GBM and anaplastic gliomas than grade 2 gliomas.[30] This interobserver variability is likely due to the non specific role of ATRX in higher grade gliomas.

ATRX status has been documented to show correlation with patient age,tumor histopathology and prognosis.It confers a better progression free survival and overall survival in low grade glioma harboring IDH mutations without 1p/q19 co-deletion.[31]

Liu XY and colleagues stated that in glioma, all mutations of ATRX are inactivating leading to loss of protein expression and are rarely found in primary GBM but are frequent in grade 2 and grade 3 tumors.[32] Loss of ATRX can also be seen in secondary glioblastoma in which ATRX mutations are associated with IDH1 and TP53 mutations.

Although ATRX is not commonly a driver mutation gene, it can induce genomic instability leading to further mutations and rearrangements. ATRX mutated cells are particularly sensitive to DNA damaging agents and this characteristic can be used therapeutically.[33]

TP53 is a tumor suppressor gene which has been mapped to chromosome 17. p53 protein binds DNA which in turn stimulates another gene to produce p21 which interacts with CDK2 inabling the cell to pass to the next cycle of division.When p53 mutations take place,p21 is not made available to provide the ‘stop signal’ and hence cell division occurs uncontrollably leading to formation of tumors. Hence p53 plays a critical role in tumor prevention by orchestrating cellular responses like damaged cell apoptosis, maintaining genomic stability, inhibition of angiogenesis,regulation of metabolism and so on.[34]

p53 is frequently mutated in glioblastoma. Although p53 mutations are oncogenic in glioblastoma, other genes must also be mutated to drive progression. GBM with p53 mutations are seen to be more invasive,proliferative and less apoptotic,Hence they are more resistant to DNA damaging therapeutic drugs.[35]

Homozygous deletion of CDKN2A/ARF locus occurring in 60% of GBM cases is the most frequently deregulated component of p53 pathway.[36] MDM2 an MDM4 are oncogenic inhibitors of p53.They are amplified in GBM leading to loss of various tumor suppressor functions such as growth arrest, apoptosis and DNA repair.

Although p53 mutations have had a consistent association with GBM, there has been inconsistency in its association with survival outcome in GBM patients. Contrary to the studies of Liu XY and colleagues, Newcomb EW and his associates concluded that survival of patients with GBM is not influenced with altered expression of p53,p16,MDM2,EGFR or Bcl2.[37]

Ki-67 is a nuclear protein persistently expressed in all phases of the cell cycle.It is widely used as a proliferation marker for human tumor cells.It is absent in resting cells.The content of cellulalr Ki-67 protein markedly increases as the cell progresses through S phase of the cell cycle.

Ki67 monoclonal antibodies and MIB antibodies were developed to target different epitopes of the Ki-67 antigen.The advantage of the MIB 1 antibody when compared to the original Ki-67 antibody is that it can be used on formalin fixed paraffin embedded sections after antigen has been retrieved through heat mediated methods.

Krishnan SS et al in their study found that there was a significant correlation between Mindbomb Homolog1 (MIB1)index and high grade glioma and suggested that MIB index can be used as a prognostic tool.[38] They reported that low MIB index (<10%) was associated with longer survival in higher grade gliomas irrespective of histological grade.

AIMS AND OBJECTIVES

1.To study the demographic profile of glioma patients coming to AIIMS Bhopal, a tertiary care center in Central India .

2.To evaluate the long term outcome of high grade glioma and its correlation with immunohistochemical markers.

3.To study the clinical evolution of IDH positive tumors

MATERIALS AND METHODS

Study Design: Hospital based observational retrospective and prospective study

Study setting: Patients diagnosed with glioma from out-patient and in-patient department for Neurosurgery, and emergency services of AIIMS Bhopal who are admitted and operated over a period of two years

Study Period: Entire study was conducted for a period of 2years from the date of obtaining ethical clearance. The retrospective data from follow-up patients of operated cases of glioma in the Neurosurgery department have been included.

Sample size: 60 patients

Sampling Technique: All patients with glioma coming to emergency and Neurosurgery OPD of AIIMS Bhopal were recruited for the study.

Study unit: Patients presenting to the Department of Neurosurgery/Emergency department with diagnosis of glioma

Inclusion criteria

1.All patients diagnosed with intracranial space occupying lesions with radiological features suggestive of glioma and biopsy proven diagnosis postoperatively.

2,All follow up patients of glioma previously operated in the Neurosurgery Department of AIIMS Bhopal

Exclusion criteria:

1.All patients who unable or unwilling to comply with the study requirements and follow up schedule

2.Absence or withdrawal of informed consent.

3.Patients with recurrent tumor.

4.Patients who had taken neoadjuvant radio or chemotherapy

5.Patients with multifocal or multicentric tumors.

6.Non operable cases and patients who are unfit for general anesthesia and surgery

Data collection: All patients presenting with glioma were be included in the study. The demographic profile of all these patients were be recorded and analyzed. Complete workup including hematological investigations and contrast enhanced MRI were done. Preanesthetic checkup was done and informed consent was taken. Patients underwent craniotomy and excision/decompression of the tumor and adequate samples were sent for histopathological examination to pathology department of AIIMS Bhopal. Paraffin blocks were collected and sent to NIMHANS Bangalore Pathology department for Immunohistochemistry and molecular status initially. When immunohistochemistry became functional in our institute, we sent the samples to our Histopathology laboratory. Based on the histopathology and IHC reports, patients with biopsy proven gliomas were segregated. Patients with high grade gliomas were followed up closely for long term outcomes. Clinical outcomes were assessed with Karnofsky Performance score (KPS) and Eastern Cooperative Oncology Group (ECOG) score at 6 months and at 1 year. Patient reported outcomes were recorded at 1 year using EORTC QLQ-BN 20 questionnaire for brain tumor and symptoms were thereby grouped and analyzed. All patients with IDH positive tumors were studied for their status, recovery and clinical condition on follow up. During their hospital stay and study period, patients were monitored according to the standard guidelines of the institute.

STATISTICAL ANALYSIS

The presentation of the Categorical variables was done in the form of number and percentage(%). On the other hand, the quantitative data were presented as the means ± SD and asmedian with 25th and 75th percentiles (interquartile range). The data normality was checkedby using Shapiro-Wilk test. The cases in which the data was not normal, we used nonparametric tests. The following statistical tests were applied for the results:

1. The association of the variables which were quantitative and not normally distributed in nature were analysed using Mann-Whitney Test and variables which were quantitative and normally distributed in nature were analysed using Independent t test.

2. The association of the variables which were qualitative in nature were analysed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used.The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was donewith the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer,Chicago, USA, ver 25.0.For statistical significance, p value of less than 0.05 was considered statistically significant.

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disable; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

ECOG	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair

RESULTS AND OBSERVATIONS

The study was conducted in Department of Neurosurgery and emergency services of AIIMS Bhopal. 60 patients diagnosed with intracranial space occupying lesions with radiological features suggestive of glioma and biopsy proven diagnosis postoperatively were included in the study. Demographic profile of gliomas, long term outcome of high grade glioma and the clinical evolution of IDH positive tumors were studied and results are as follows.

Demographic profile and general characteristics of Glioma patients

Table 1:- Age distribution.

Age	Frequency	Percentage
10 to 20 years	5	8.33%
21 to 30 years	12	20.00%
31 to 40 years	15	25.00%
41 to 50 years	13	21.67%
51 to 60 years	11	18.33%
61 to 70 years	4	6.67%
Mean ± SD	39.45 ± 14.1	
Median(25th-75th percentile)	39.5(30-50.25)	
Range	10-70	

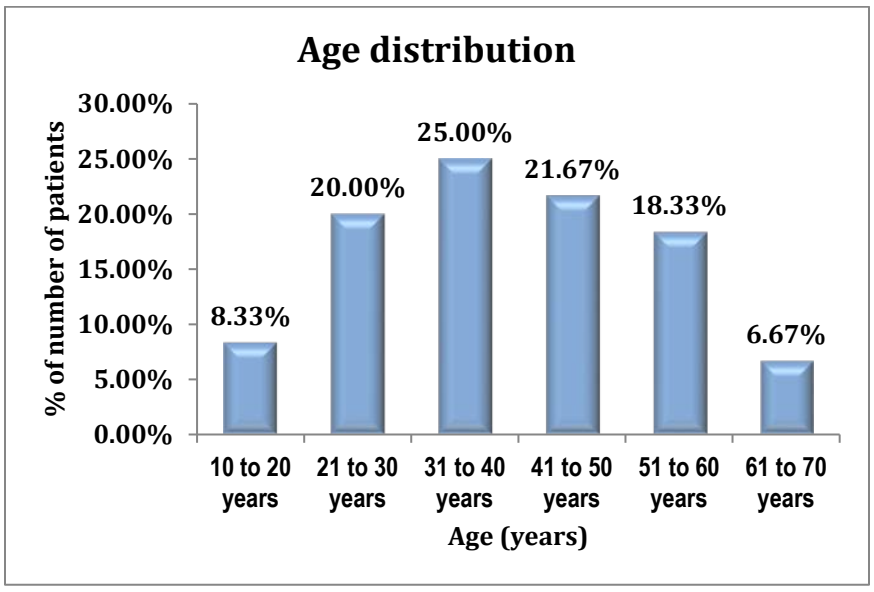

Figure 1:- Age distribution.

Distribution of age among the study subjects was as follows: 15 (25.00%) cases were aged 31 to 40 years, 13 (21.67%) cases were aged 41 to 50 years, 12 (20.00%) cases were aged 21 to 30 years, 11 (18.33%) cases were aged 51 to 60 years, 5 (8.33%) cases were aged 10 to 20 years and 4 (6.67%) cases were aged 61 to 70 years. Mean age was 39.45 ± 14.1 years with median (25th-75th percentile) of 39.5 (30-50.25) years (Table 1, Figure 1).

Table 2:- Gender distribution.

Gender	Frequency	Percentage
Female	16	26.67%
Male	44	73.33%
Total	60	100.00%

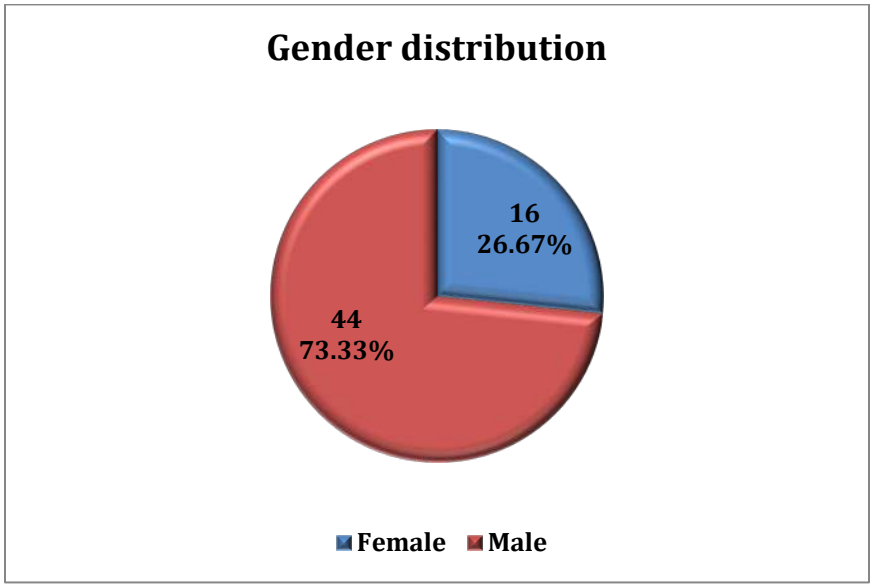

Figure 2:- Gender distribution.

Distribution of gender among the study subjects was as follows: 44 (73.33%) were males and 16 (26.67%) were females (Table 2, Figure 2).

Table 3:- Clinical symptomatology distribution.

Clinical symptomatology	Frequency	Percentage
Seizures	24	40.00%
Headache	13	21.67%
Motor weakness	13	21.67%
Visual disturbance	9	15.00%
Aphasia and dementia	1	1.67%
Total	60	100.00%

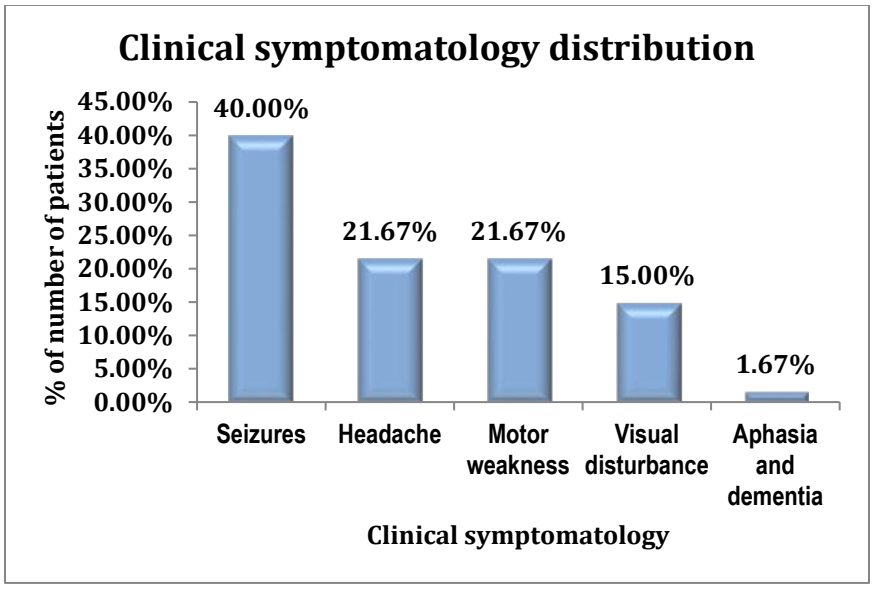

Figure 3:- Clinical symptomatology distribution.

Distribution of clinical symptomatology among the study subjects was as follows: 24 (40.00%) cases had seizures, 13 (21.67%) cases had headache, 13 (21.67%) cases had motor weakness, 9 (15.00%) cases had visual disturbance and 1 (1.67%) case had aphasia and dementia (Table 3, Figure 3).

Table 4:- Neurological deficit distribution.

Neurological deficit	Frequency	Percentage
Absent	23	38.33%
Present	37	61.67%
Total	60	100.00%

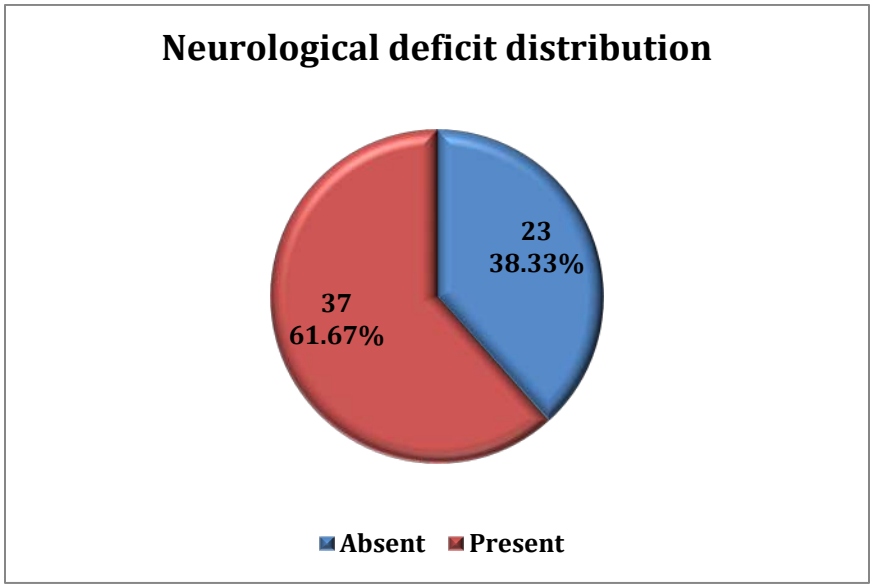

Figure 4:- Neurological deficit distribution.

Distribution of neurological deficit among the study subjects was as follows: 37 (61.67%) cases had neurological deficit while 23 (38.33%) cases did not have neurological deficit on presentation. (Table 4, Figure 4).

Table 5:- Lobe distribution.

Lobe	Frequency	Percentage
Left frontal	11	18.33%
Left temporal	4	6.67%
Left parietal	3	5.00%
Left parieto-occipital	2	3.33%
Left thalamic	2	3.33%
Left frontotemporal	2	3.33%
Left insular	1	1.67%
Left occipital	1	1.67%
Right frontal	8	13.33%
Right temporal	7	11.67%
Right frontotemporal	3	5.00%
Right frontoparietal	2	3.33%
Right parietal	2	3.33%
Right parieto-occipital	2	3.33%
Right frontotemporoinsular	1	1.67%
Right frontotemporoparietal	1	1.67%
Right insular	1	1.67%
Right parietotemporal	2	3.33%
Septum pellucidum	1	1.67%
Suprasellar	1	1.67%
4th ventricle	1	1.67%
Cerebral peduncle	1	1.67%
Corpus callosum	1	1.67%
Total	60	100.00%

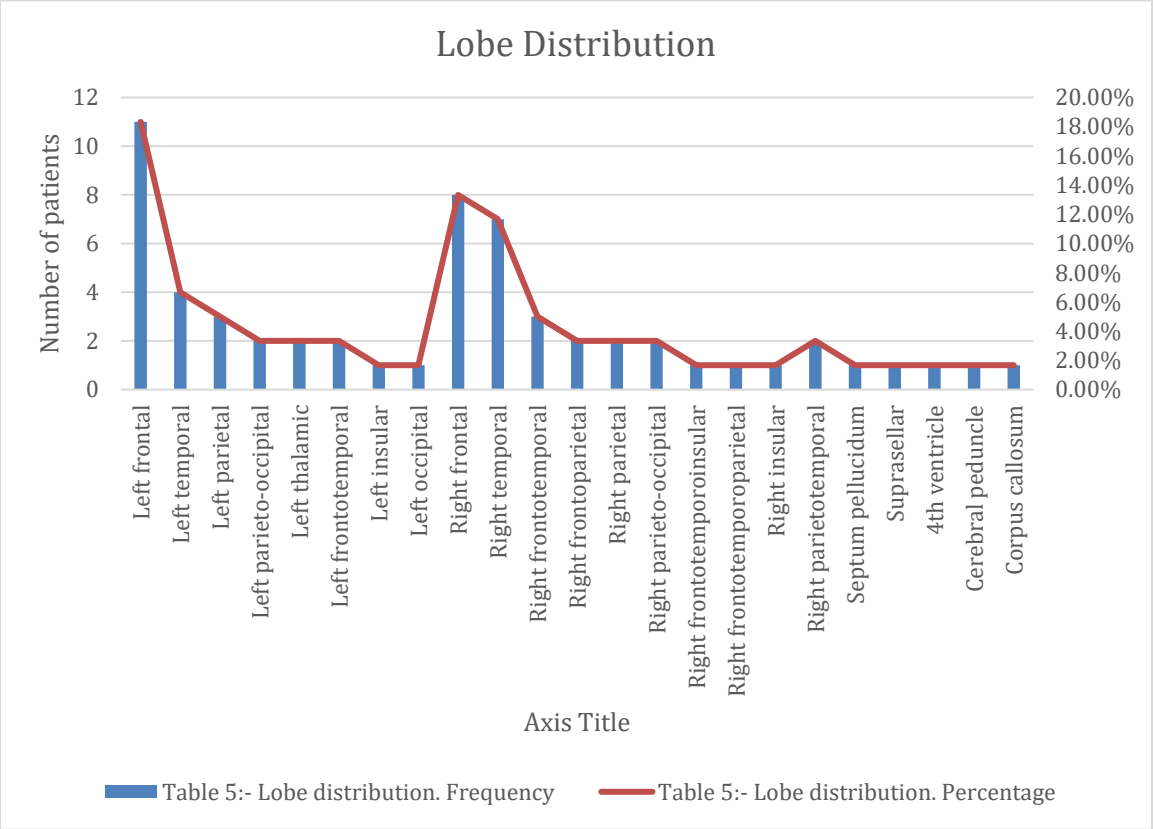

Figure 5:- Lobe distribution.

Distribution of lobe among the study subjects was as follows: 11 (18.33%) cases were left frontal, 8 (13.33%) cases were right frontal, 7 (11.67%) cases were right temporal, 4 (6.67%) cases were left temporal, 3 (5.00%) cases were left parietal, 3 (5.00%) cases were right frontotemporal, 2 (3.33%) cases each were left parieto-occipital, left thalamic, left frontotemporal, right frontoparietal, right parietal and right parieto-occipital and right parietotemporal and 1 (1.67%) case each involved left insular, left occipital, right frontotemporoinsular, right frontotemporoparietal, right insular, right temporoparietal, septum pellucidum, suprasellar, 4th ventricle, cerebral peduncle and corpus callosum (Table 5, Figure 5).

Table 6:- Region distribution.

Region	Frequency	Percentage
Lateral brain/hemispheric	53	88.33%
Midline	5	8.33%
Thalamic	2	3.33%
Total	60	100.00%

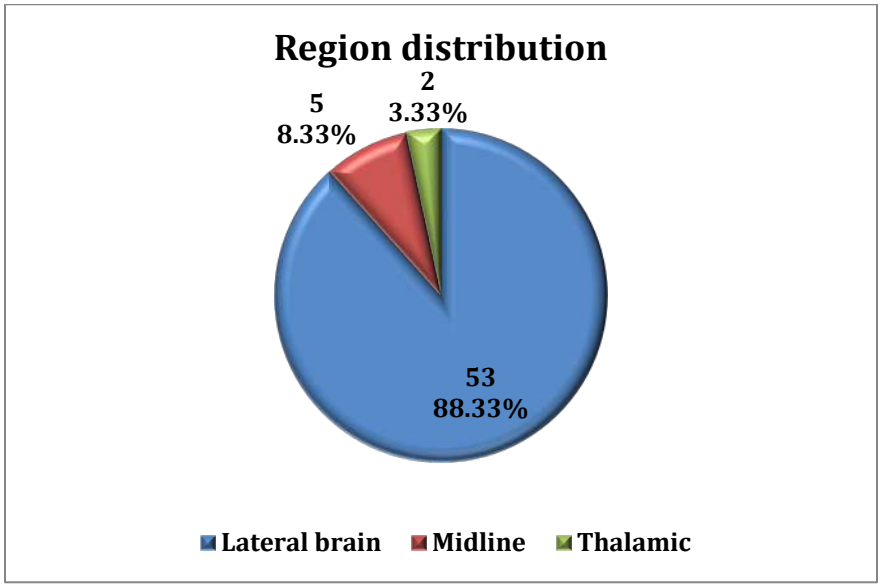

Figure 6:- Region distribution.

Distribution of region among the study subjects was as follows: 53 (88.33%) cases were in lateral brain/hemispheric, 5 (8.33%) cases were in midline and 2 (3.33%) cases were thalamic (Table 6, Figure 6).

Table 7:- WHO grade distribution.

WHO grade	Frequency	Percentage
Grade I	5	8.33%
Grade II	14	23.33%
Grade III	13	21.67%
Grade IV	28	46.67%
Total	60	100.00%

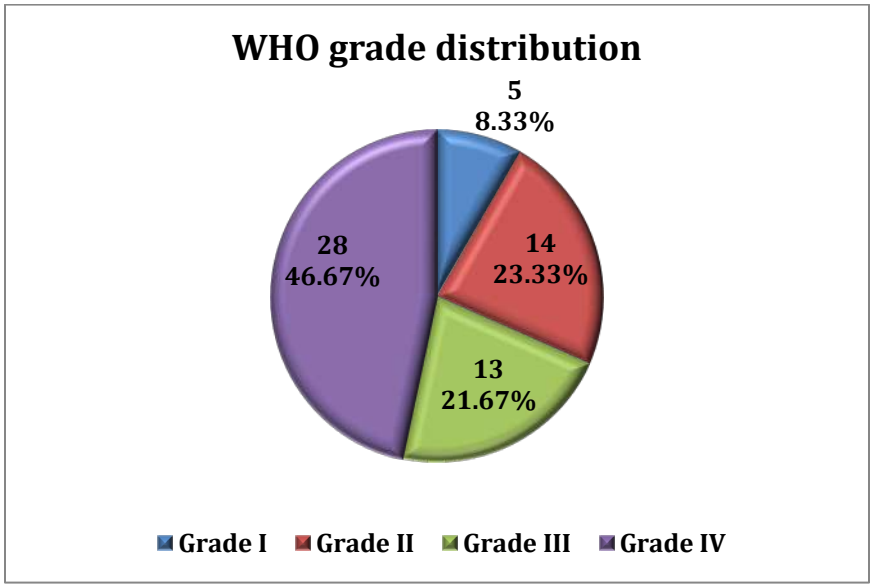

Figure 7:- WHO grade distribution.

Distribution of WHO grade among the study subjects was as follows: 28 (46.67%) cases had grade IV, 14 (23.33%) cases had grade II, 13 (21.67%) cases had grade III and 5 (8.33%) cases had grade I (Table 7, Figure 7).

Table 8:- Grading of glioma distribution.

Grading of glioma	Frequency	Percentage
Low	15	25.00%
High	45	75.00%
Total	60	100.00%

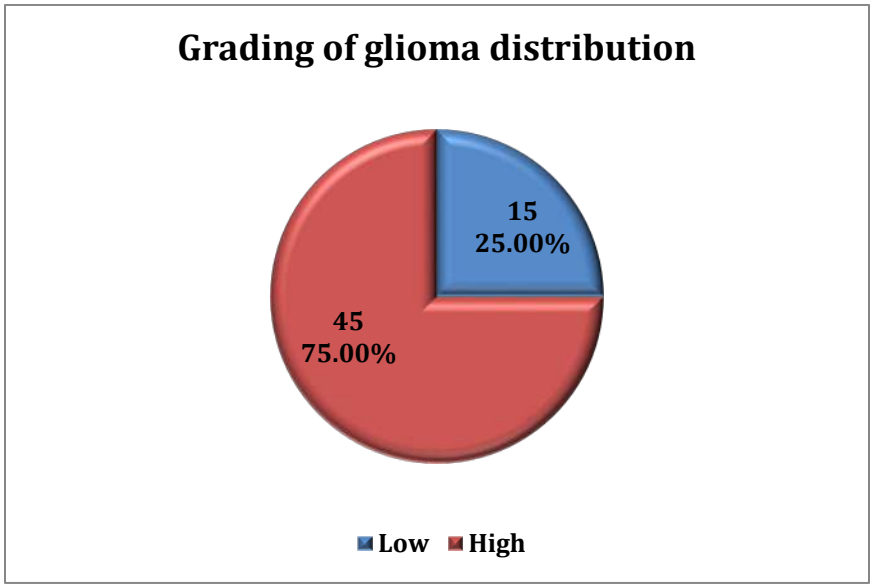

Figure 8:- Grading of glioma distribution.

Grading of glioma among the study subjects was as follows: 45 (75.00%) cases had high grade and 15 (25.00%) cases had low grade (Table 8, Figure 8).

Table 9:- IDH status distribution.

IDH status	Frequency	Percentage
Negative	38	63.33%
Positive	22	36.67%
Total	60	100.00%

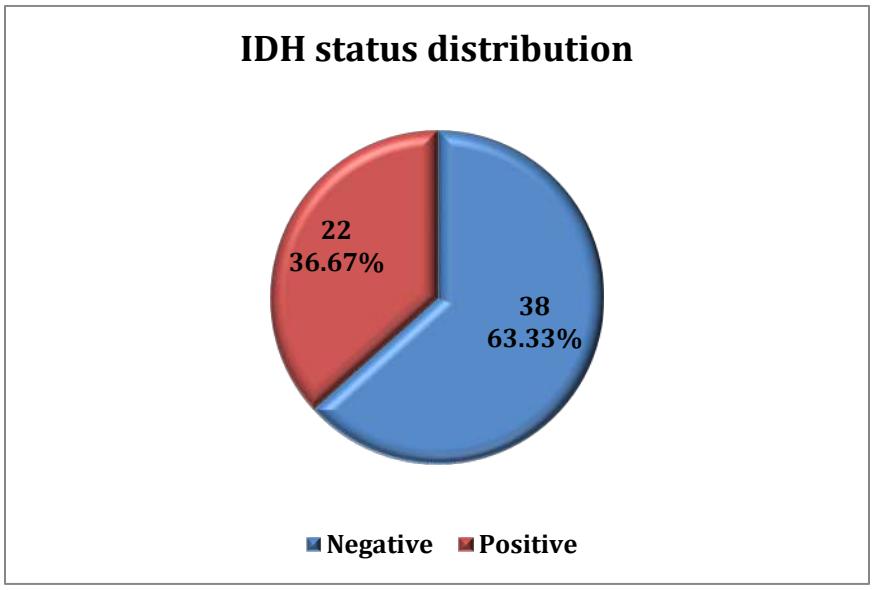

Figure 9:- IDH status distribution.

Distribution of IDH status among the study subjects was as follows: 38 (63.33%) cases were negative and 22 (36.67%) cases were positive (Table 9, Figure 9).

Table 10:- ATRX status distribution.

ATRX status	Frequency	Percentage
Retained nuclear expression	44	73.33%
Loss of expression	16	26.67%
Total	60	100.00%

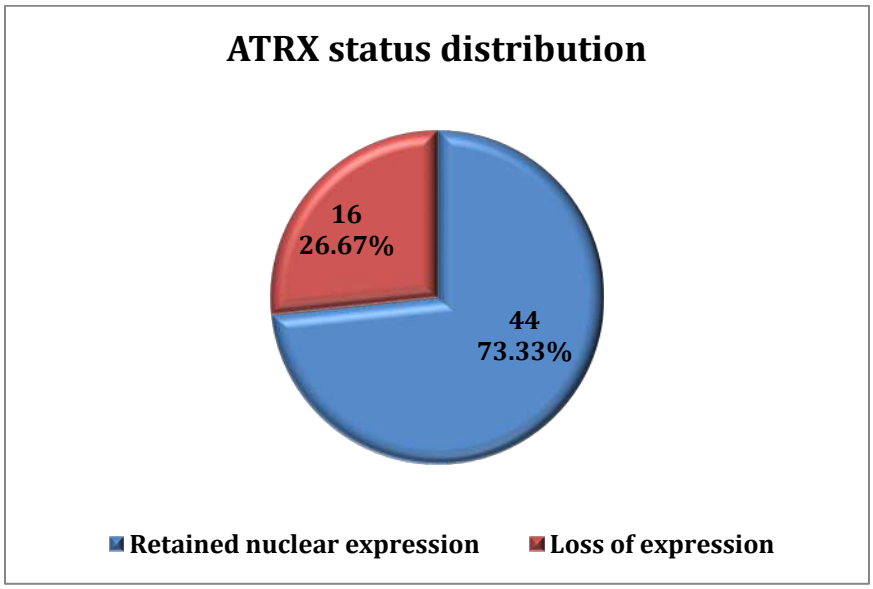

Figure 10:- ATRX status distribution.

ATRX status showed that 44 (73.33%) cases had retained nuclear expression while 16 (26.67%) cases had loss of expression (Table 10, Figure 10).

Table 11:- P53 status distribution.

P53 status	Frequency	Percentage
Negative	37	61.67%
Positive	23	38.33%
Total	60	100.00%

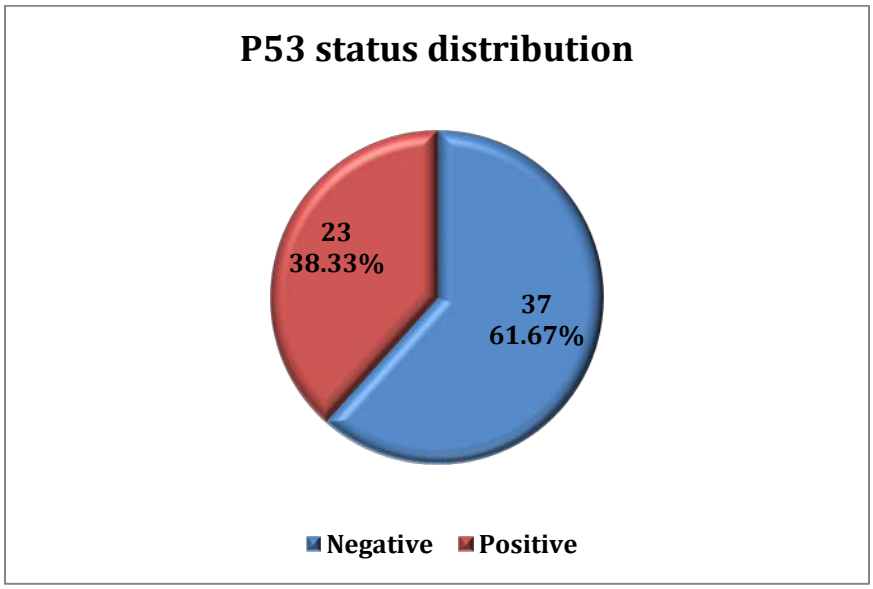

Figure 11:- P53 status distribution.

Distribution of P53 status among the study subjects was as follows: 37 (61.67%) cases were negative and 23 (38.33%) cases were positive (Table 11, Figure 11).

Table 12:- MIB1 index distribution.

MIB1 index	Frequency	Percentage
0% to 5%	18	30.00%
>5% to 10%	16	26.67%
>10% to 15%	14	23.33%
>15% to 20%	11	18.33%
>20%	1	1.67%
Total	60	100.00%

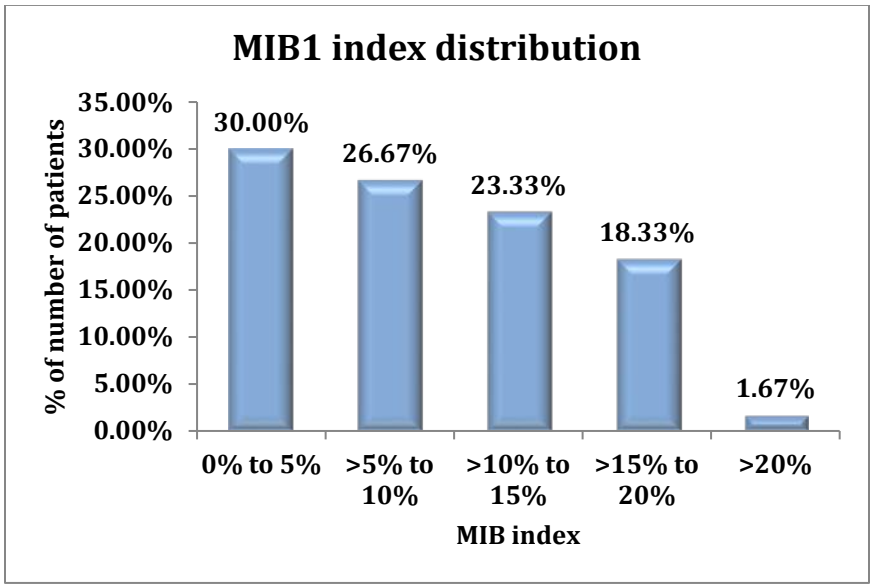

Figure 12:- MIB1 index distribution.

Distribution of MIB1 index among the study subjects was as follows: 18 (30.00%) cases had 0% to 5%, 16 (26.67%) cases had >5% to 10%, 14 (23.33%) cases had >10% to 15%, 11 (18.33%) cases had >15% to 20% and 1 (1.67%) case had >20% (Table 12, Figure 12).

Table 13:- Olig2 distribution.

Olig2	Frequency	Percentage
Negative	37	61.67%
Positive	23	38.33%
Total	60	100.00%

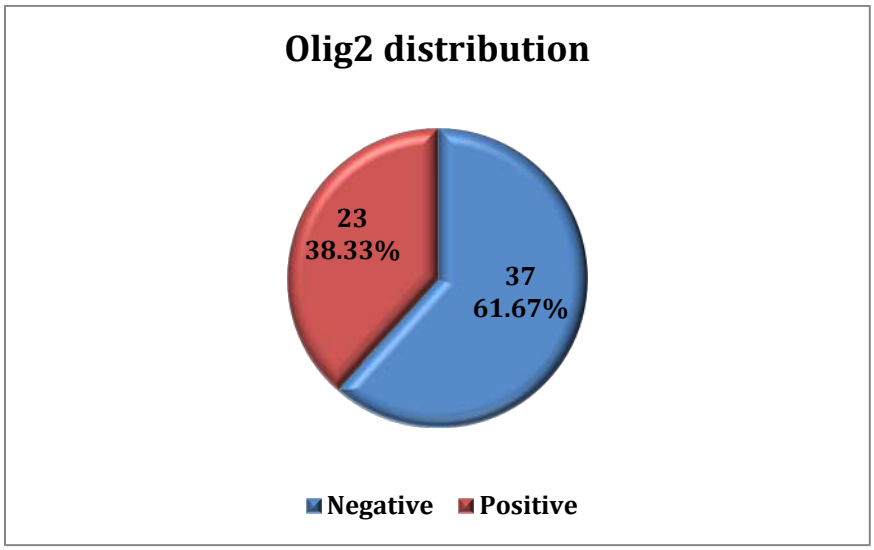

Figure 13:- Olig2 distribution.

Distribution of Olig2 status among the study subjects was as follows: 37 (61.67%) cases were negative and 23 (38.33%) cases were positive (Table 13, Figure 13).

Table 14:- GFAP distribution.

GFAP	Frequency	Percentage
Negative	51	85.00%
Positive	9	15.00%
Total	60	100.00%

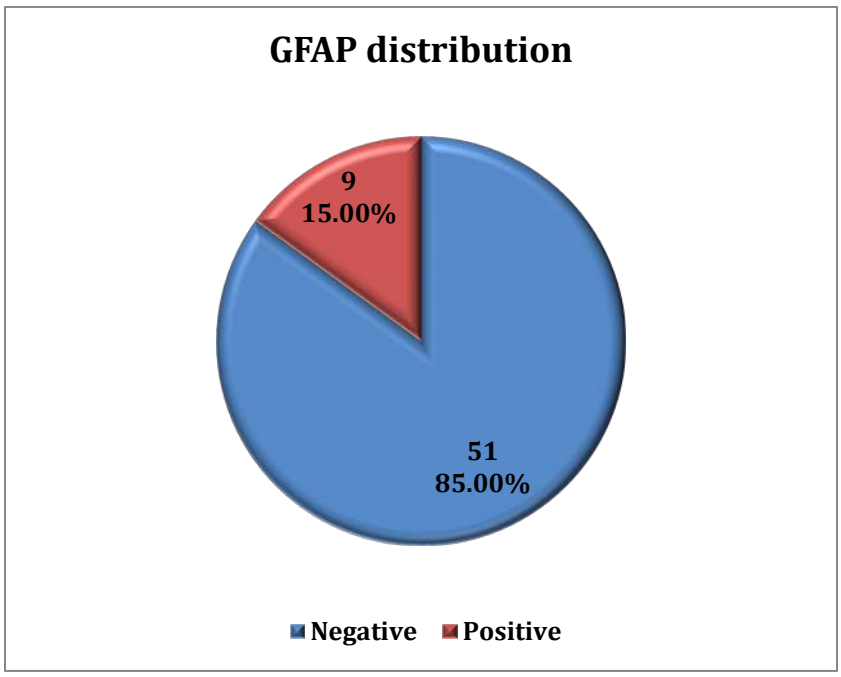

Figure 14:- GFAP distribution.

Distribution of GFAP status among the study subjects was as follows: 51 (85.00%) cases were negative and 9 (15.00%) cases were positive (Table 14, Figure 14).

Table 15:- Tumor type on HPR.

Tumor type on HPR	Frequency	Percentage
Glioblastoma	24	40.00%
Astrocytoma	11	18.33%
Oligodendroglioma	10	16.67%
Pilocytic astrocytoma	3	5.00%
Oligoastrocytoma	2	3.33%
Anaplastic oligodendroglioma	2	3.33%
Diffuse adult glioma	2	3.33%
Diffuse astrocyticglioma	2	3.33%
Diffuse midline glioma	1	1.67%
Ependymoma	1	1.67%
Ganglioglioma	1	1.67%
Low grade glioma NOS	1	1.67%
Total	60	100.00%

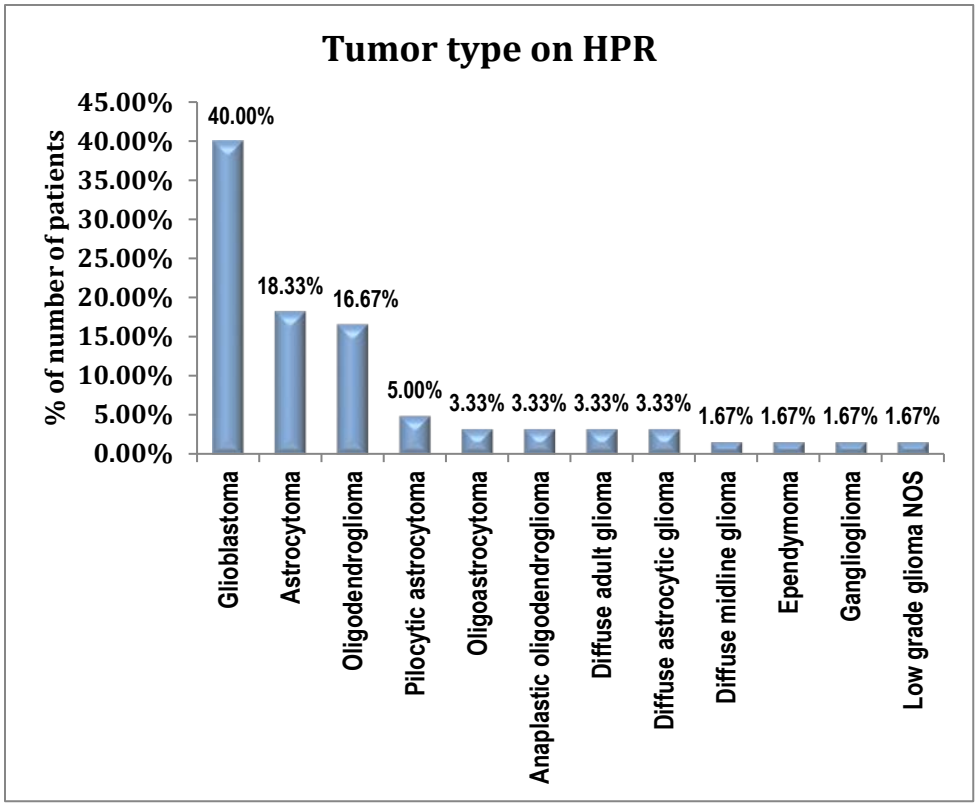

Figure 15:- Tumor type on HPR

Distribution of impression among the study subjects was as follows: 24 (40.00%) cases had glioblastoma, 11 (18.33%) cases had astrocytoma, 10 (16.67%) cases had oligodendroglioma, 3

(5.00%) cases had pilocytic astrocytoma, 2 (3.33%) cases each had oligoastrocytoma, anaplastic oligodendroglioma, diffuse adult glioma and diffuse astrocytic glioma, and 1 (1.67%) case each had diffuse midline glioma, ependymoma, ganglioglioma and low-grade glioma NOS (Table 15, Figure 15).

Table 16:- Surgical resection distribution.

Surgical resection	Frequency	Percentage
Subtotal resection of tumor	4	6.67%
Gross total excision	56	93.33%
Total	60	100.00%

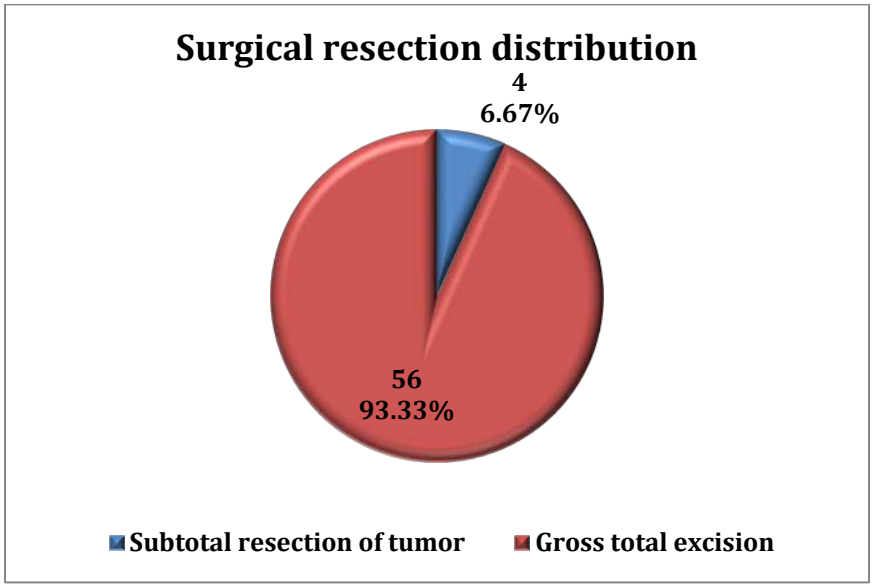

Figure 16:- Surgical resection distribution.

Distribution of surgical resection among the study subjects was as follows: 56 (93.33%) cases had gross total excision and 4 (6.67%) cases had subtotal resection of tumor (Table 16, Figure 16).

Table 17:- Radiotherapy distribution.

Radiotherapy	Frequency	Percentage
No	14	23.33%
Yes	46	76.67%
Total	60	100.00%

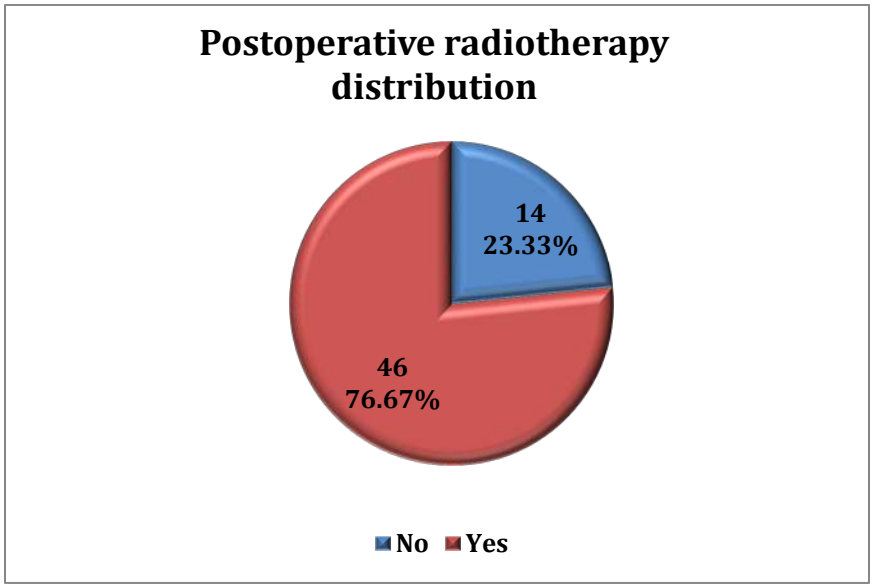

Figure 17:- Postoperative radiotherapy distribution.

Distribution of postoperative radiotherapy among the study subjects was as follows: 46 (76.67%) cases received radiotherapy and 14 (23.33%) cases did not undergo treatment (Table 17, Figure 17).

Table 18:-Postoperative chemotherapy distribution.

Chemotherapy	Frequency	Percentage
No	25	41.67%
Yes	35	58.33%
Total	60	100.00%

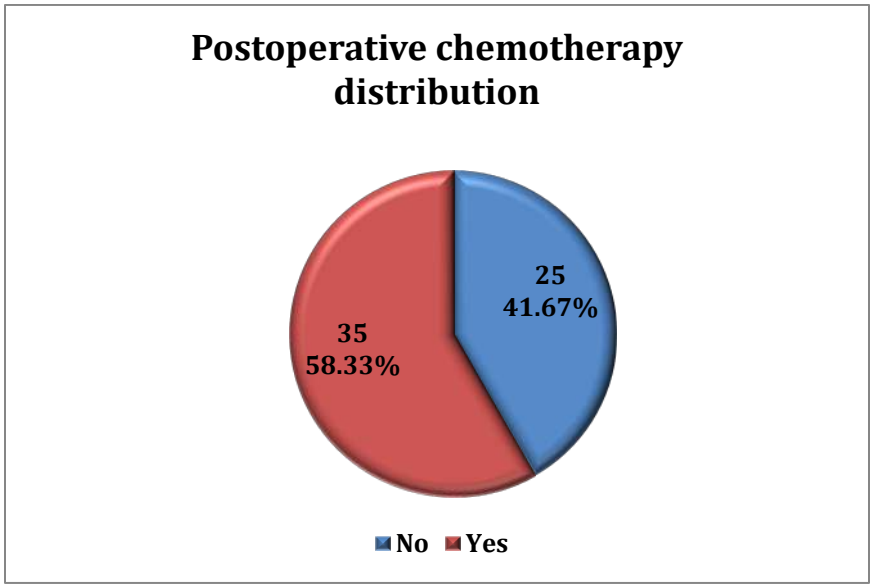

Figure 18:- Chemotherapy distribution.

Distribution of postoperative chemotherapy among the study subjects was as follows: 35 (58.33%) cases received chemotherapy while 25 (41.67%) cases did not undergo treatment (Table 25, Figure 25).

Table 19:- Descriptive statistics of overall survival.

Variable	Mean ± SD	Median(25th-75th percentile)	Range
Overall survival (months)	11.62 ± 5.54	14(6.75-16)	1-19

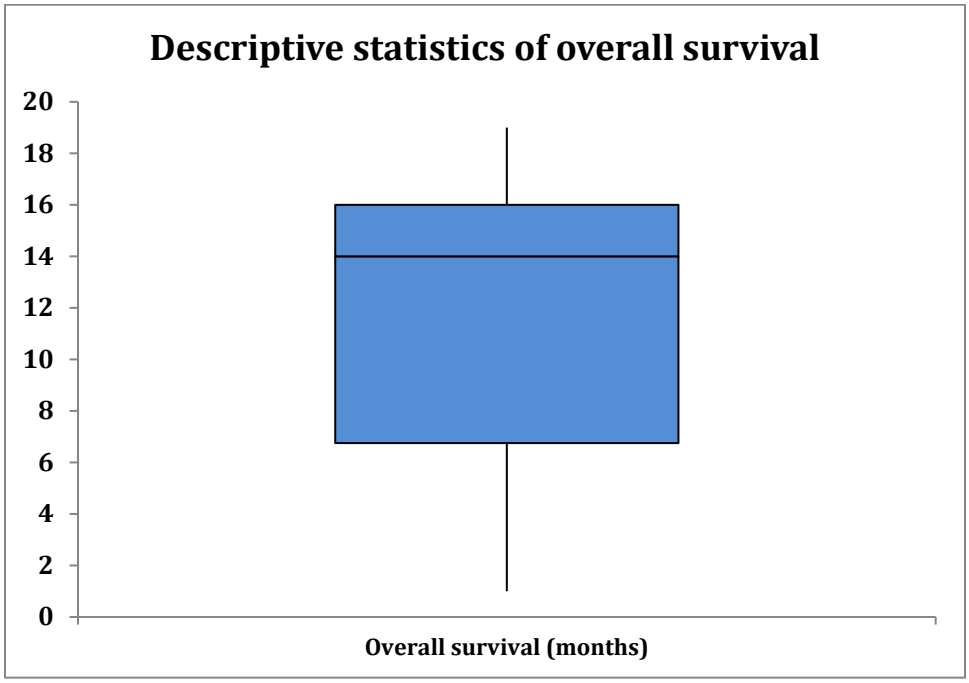

Figure 19:-Descriptive statistics of overall survival (months).

Mean value of overall survival was 11.62 ± 5.54 months, with median (25th-75th percentile) of 14 (6.75-16) months (Table 26, Figure 26).

Table 20:- Clinician reported outcomes: KPS and ECOG distribution.

KPS and ECOG	Frequency	Percentage
ECOG at 6 months		
0	16	29.09%
1	23	41.82%
2	10	18.18%
3	2	3.64%
4	4	7.27%
ECOG at 1year		
0	12	23.53%
1	20	39.22%
2	6	11.76%
3	4	7.84%
4	9	17.65%
KPS at 6 months		
Mean ± SD	79.27 ± 23.16	
Median(25th-75th percentile)	80(60-100)	
Range	10-100	
KPS at 1year		
Mean ± SD	71.57 ± 30.16	
Median(25th-75th percentile)	80(50-100)	
Range	10-100	

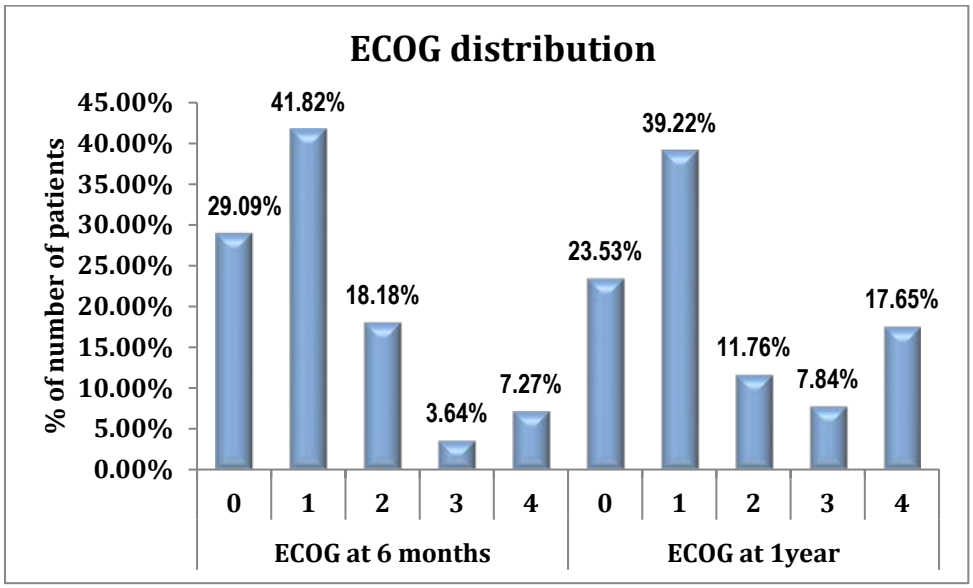

Figure 20.1:- Clinician reported outcomes: ECOG distribution.

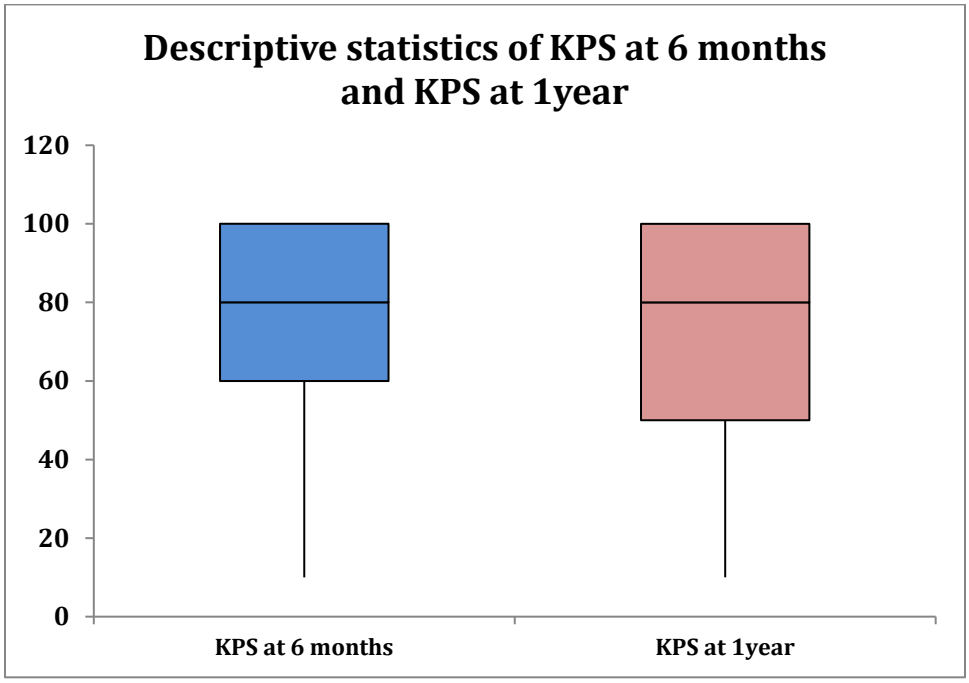

Figure 20.2:-Clinician reported outcomes: Descriptive statistics of KPS at 6 months and KPS at 1year.

Clinician reported outcomes

Distribution of ECOG at 6 months among the study subjects was as follows: 23 (41.82%) cases had grade 1, 16 (29.09%) cases had grade 0, 10 (18.18%) cases had grade 2, 4 (7.27%) cases had grade 4 and 2 (3.64%) cases had grade 3. Distribution of ECOG at 1 year was as follows: 20 (39.22%) cases had grade 1, 12 (23.53%) cases had grade 0, 9 (17.65%) cases had grade 4, 6 (11.76%) cases had grade 2 and 4 (7.84%) cases had grade 3.

Mean values of KPS at 6 months and at 1 year among the study subjects were 79.27 ± 23.16 and 71.57 ± 30.16 with medians (25th-75th percentile) of 80 (60-100) and 80 (50-100) respectively (Table 20, Figures 20.1 and 20.2).

Table 21:- Patient reported outcomes: Symptoms at 1 year distribution.

Symptoms at 1 year	Frequency	Percentage
BFU(Future uncertainty)	23	45.10%
BVD (Visual disorder)	14	27.45%
BMD(Motor deficit)	26	50.98%
BCD(Communication deficit)	18	35.29%
BHA(Headaches)	13	25.49%
BSE(Seizures)	4	7.84%
BDR(Drowsiness)	18	35.29%
BBC (Loss of bladder control)	13	25.49%
BHL (Hair loss)	18	35.29%
BWL (Weakness in lower limbs)	36	70.59%
BIS (Itchy skin)	13	25.49%

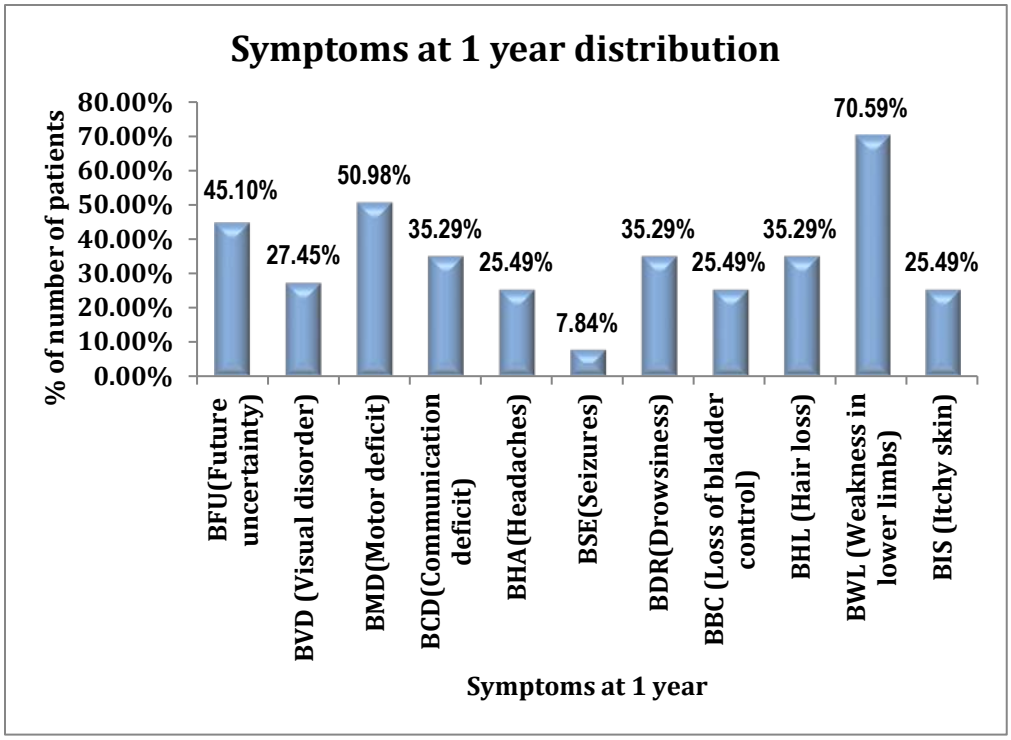

Figure 21:-Patient reported outcomes: Symptoms at 1 year distribution.

Patient reported outcomes:

Distribution of symptoms at 1 year among the study subjects was as follows: 36 (70.59%) cases had BWL (weakness in lower limbs), 26 (50.98%) cases had BMD (motor deficit), 23 (45.10%) cases had BFU (future uncertainty), 18 (35.29%) cases each had BCD (communication deficit), BDR (drowsiness) and BHL (hair loss), 14 (27.45%) cases had BVD (visual disorder), 13 (25.49%) cases each had BHA (headaches), BBC (loss of bladder control) and BIS (itchy skin), and 4 (7.84%) cases had BSE (seizures) (Table 21, Figure 21).

Long term outcomes of high grade glioma

Table 22:-Association of age with grading of glioma.

Age	Low(n=15)	High(n=45)	Total	P value
10 to 20 years	5 (33.33%)	0 (0%)	5 (8.33%)	0.0008*
21 to 30 years	4 (26.67%)	8 (17.78%)	12 (20%)	
31 to 40 years	4 (26.67%)	11 (24.44%)	15 (25%)	
41 to 50 years	2 (13.33%)	11 (24.44%)	13 (21.67%)	
51 to 60 years	0 (0%)	11 (24.44%)	11 (18.33%)	
61 to 70 years	0 (0%)	4 (8.89%)	4 (6.67%)	
Mean ± SD	26.67 ± 11.19	43.71 ± 12.38	39.45 ± 14.12	<.0001‡
Median(25th-75th percentile)	23(18-35.5)	42(35-52)	39.5(30-50.25)	
Range	10-45	21-70	10-70	

‡ **Independent t test,** * **Fisher's exact test**

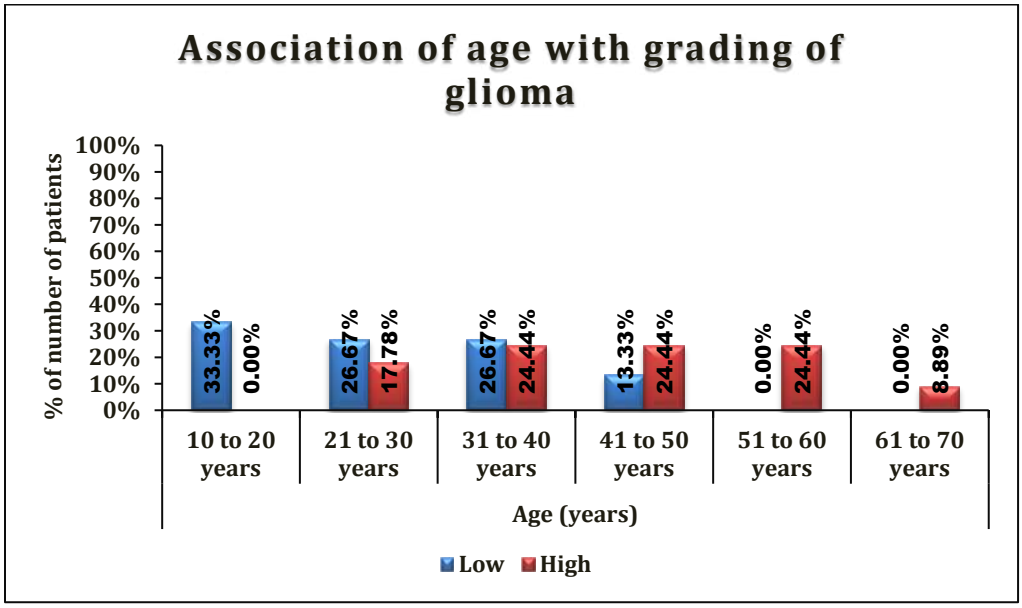

Figure 22:-Association of age with grading of glioma.

Compared to low grading group, high grading group had significantly lower proportion of patients aged 10 to 20 years (0% vs. 33.33%), 21 to 30 years (17.78% vs. 26.67%) and 31 to 40 years (24.44% vs. 26.67%). Conversely, proportion of patients aged 41 to 50 years (24.44% vs. 13.33%), 51 to 60 years (24.44% vs. 0%) and 61 to 70 years (8.89% vs. 0%) was significantly higher in high grading compared to low grading (p value = 0.0008).

Mean ± SD of age in high grading group was 43.71 ± 12.38 years, which was significantly higher compared to low grading group (26.67 ± 11.19 years) (p value < 0.0001) (Table 22, Figure 22).

Table 23:-Association of region with grading of glioma.

Region	Low(n=15)	High(n=45)	Total	P value
Lateral brain	12 (80%)	41 (91.11%)	53 (88.33%)	0.149*
Midline	3 (20%)	2 (4.44%)	5 (8.33%)	
Thalamic	0 (0%)	2 (4.44%)	2 (3.33%)	
Total	15 (100%)	45 (100%)	60 (100%)	

* **Fisher's exact test**

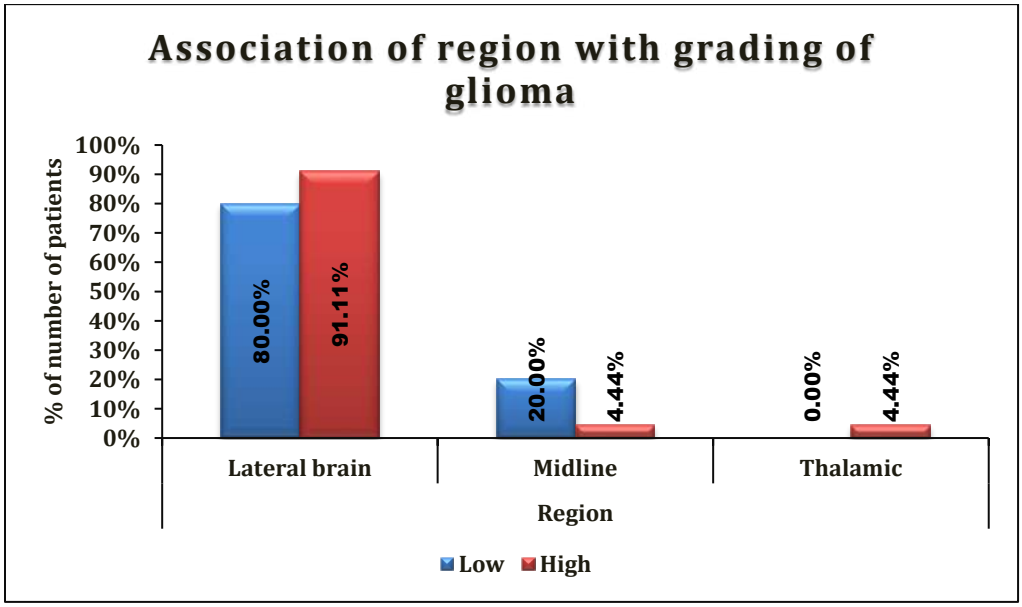

Figure 23:-Association of region with grading of glioma.

Compared to low grading group, high grading group had comparable distribution of region: lateral brain in 91.11% of high group vs. 80% of low group, midline in 4.44% vs. 20% and thalamic in 4.44% vs. 0% respectively (p value = 0.149) (Table 23, Figure 23).

Table 24:-Clinician reported outcomes: Association of KPS and ECOG with grading of glioma.

KPS and ECOG	Low	High	Total	P value
ECOG at 6 months				
0	13 (86.67%)	3 (7.50%)	16 (29.09%)	<.0001*
1	1 (6.67%)	22 (55%)	23 (41.82%)	
2	1 (6.67%)	9 (22.50%)	10 (18.18%)	
3	0 (0%)	2 (5%)	2 (3.64%)	
4	0 (0%)	4 (10%)	4 (7.27%)	
ECOG at 1year				
0	11 (73.33%)	1 (2.78%)	12 (23.53%)	<.0001*
1	2 (13.33%)	18 (50%)	20 (39.22%)	
2	2 (13.33%)	4 (11.11%)	6 (11.76%)	
3	0 (0%)	4 (11.11%)	4 (7.84%)	
4	0 (0%)	9 (25%)	9 (17.65%)	
KPS at 6 months				
Mean ± SD	96.67 ± 9	72.75 ± 23.53	79.27 ± 23.16	<.0001‡
Median(25th-75th percentile)	100(100-100)	80(60-90)	80(60-100)	
Range	70-100	10-100	10-100	
KPS at 1year				
Mean ± SD	92 ± 14.74	63.06 ± 30.97	71.57 ± 30.16	<.0001‡
Median(25th-75th percentile)	100(90-100)	80(40-90)	80(50-100)	
Range	60-100	10-100	10-100	

‡ Independent t test, * Fisher's exact test

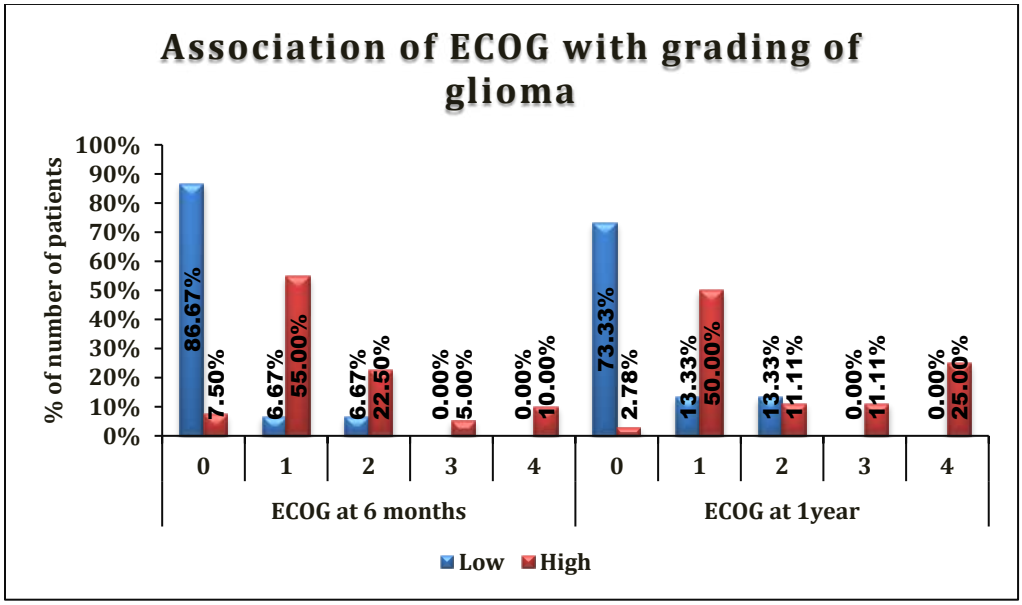

Figure 24.1:-Association of ECOG with grading of glioma.

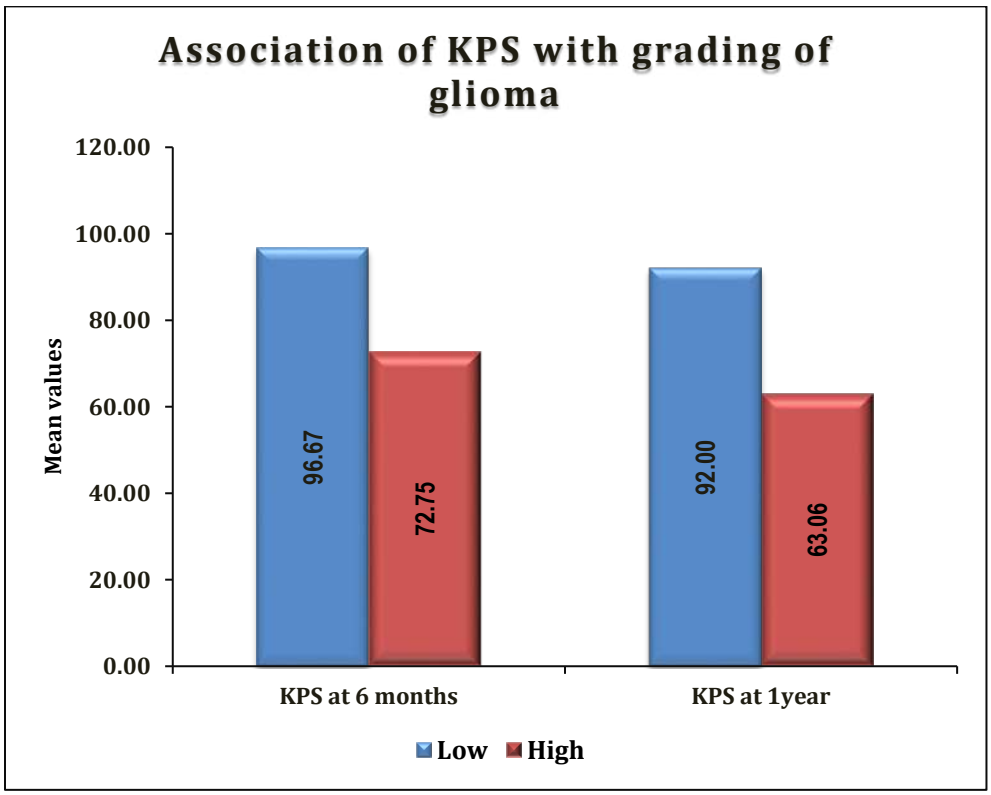

Figure 24.2:-Association of KPS with grading of glioma.

Clinician reported outcomes

Compared to low grading group, high grading group had significantly lower proportion of patients with ECOG score 0 at 6 months (7.5% vs. 86.67%) and significantly higher proportion with ECOG scores of 1 (55% vs. 6.67%), 2 (22.5% vs. 6.67%), 3 (5% vs. 0%) and 4 (10% vs. 0%) (p value < 0.0001).

For ECOG at 1 year, high grading group had significantly higher proportions with scores of 1 (50% vs. 13.33%), 3 (11.11% vs. 0%) and 4 (25% vs. 0%) and significantly lower proportions with scores of 0 (2.78% vs. 73.33%) and 2 (11.11% vs. 13.33%) (p value < 0.0001).

KPS at 6 months and KPS at 1 year were significantly associated with glioma grading (p value < 0.05). Mean ± SD of KPS at 6 months and 1 year was significantly lower in high grading group (72.75 ± 23.53 vs. 96.67 ± 9, p value < 0.0001; 63.06 ± 30.97 vs. 92 ± 14.74, p value < 0.0001) compared to low grading group (Table 24, Figures 24.1 and 24.2).

Table 25:-Patient reported outcomes: Association of symptoms at 1 year with grading of glioma.

Symptoms at 1 year	Low(n=15)	High(n=36)	Total	P value
BFU(Future uncertainty)	1 (6.67%)	22 (61.11%)	23 (45.10%)	0.0004*
BVD (Visual disorder)	2 (13.33%)	12 (33.33%)	14 (27.45%)	0.184*
BMD(Motor deficit)	2 (13.33%)	24 (66.67%)	26 (50.98%)	0.0006*
BCD(Communication deficit)	1 (6.67%)	17 (47.22%)	18 (35.29%)	0.009*
BHA(Headaches)	0 (0%)	13 (36.11%)	13 (25.49%)	0.006*
BSE(Seizures)	0 (0%)	4 (11.11%)	4 (7.84%)	0.307*
BDR(Drowsiness)	1 (6.67%)	17 (47.22%)	18 (35.29%)	0.009*
BBC (Loss of bladder control)	0 (0%)	13 (36.11%)	13 (25.49%)	0.006*
BHL (Hair loss)	0 (0%)	18 (50%)	18 (35.29%)	0.0004*
BWL (Weakness in lower limbs)	3 (20%)	33 (91.67%)	36 (70.59%)	<.0001*
BIS (Itchy skin)	2 (13.33%)	11 (30.56%)	13 (25.49%)	0.297*

* **Fisher's exact test**

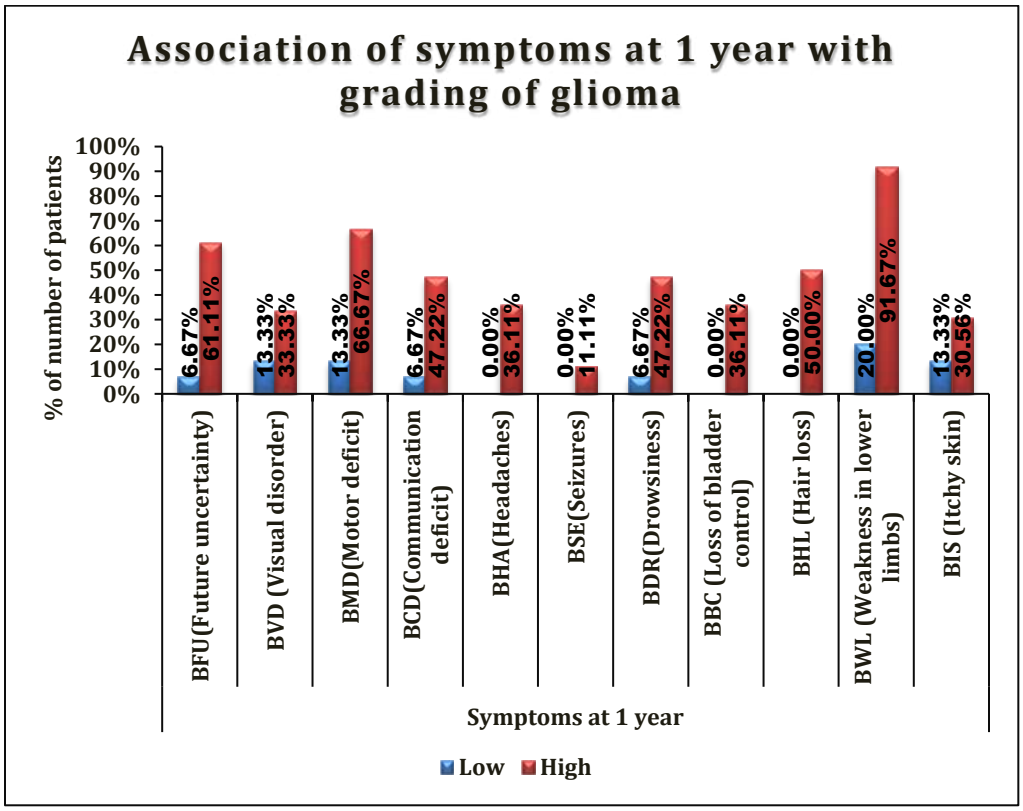

Figure 25:-Patient reported outcomes: Association of symptoms at 1 year with grading of glioma.

Compared to low grading group, high grading group had significantly higher proportion of patients experiencing various symptoms at 1 year: future uncertainty (61.11% vs. 6.67%, p value = 0.0004), motor deficit (66.67% vs. 13.33%, p value = 0.0006), communication deficit (47.22% vs. 6.67%, p value = 0.009), headaches (36.11% vs. 0%, p value = 0.006), drowsiness (47.22% vs. 6.67%, p value = 0.009), loss of bladder control (36.11% vs. 0%, p value = 0.006), hair loss (50% vs. 0%, p value = 0.0004) and weakness in lower limbs (91.67% vs. 20%, p value < 0.0001).

There was no significant difference between groups for visual disorder (33.33% in high group vs. 13.33% in low group, p value = 0.184), seizures (11.11% vs. 0%, p value = 0.307) or itchy skin (30.56% vs. 13.33%, p value = 0.297) (Table 25, Figure 25).

Table 26:-Association of outcome with grading of glioma.

Outcome	Low	High	Total	P value
Outcome				
Alive	15 (100%)	21 (46.67%)	36 (60%)	0.0001*
Died	0 (0%)	24 (53.33%)	24 (40%)	
Overall survival(months)				
Mean ± SD	-	11.62 ± 5.54	11.62 ± 5.54	NA
Median(25th-75th percentile)	-	14(6.75-16)	14(6.75-16)	
Range	-	1-19	1-19	

* **Fisher's exact test**

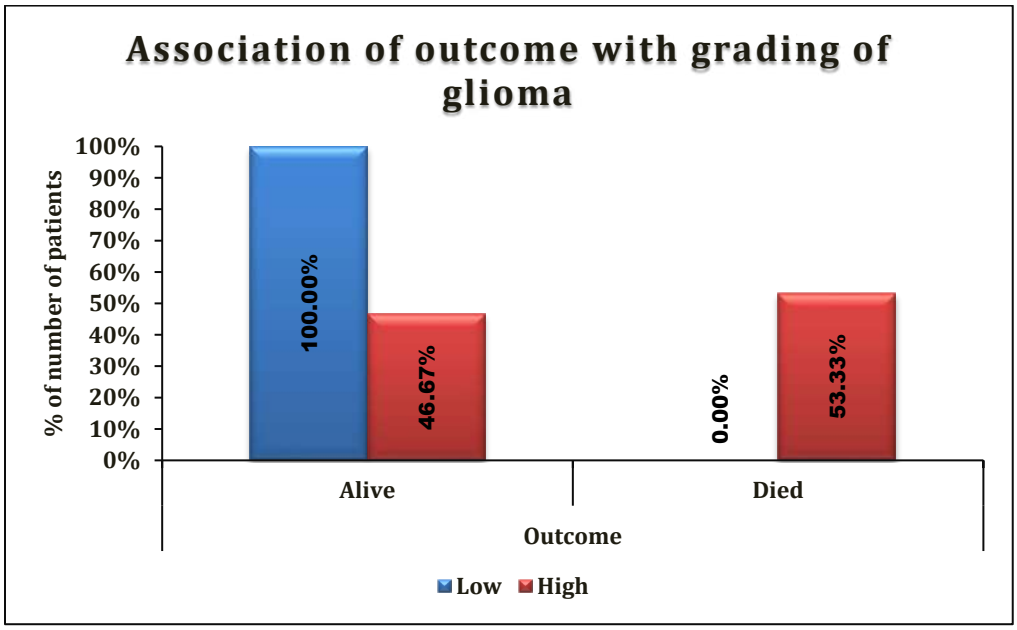

Figure 26.1:-Association of outcome with grading of glioma

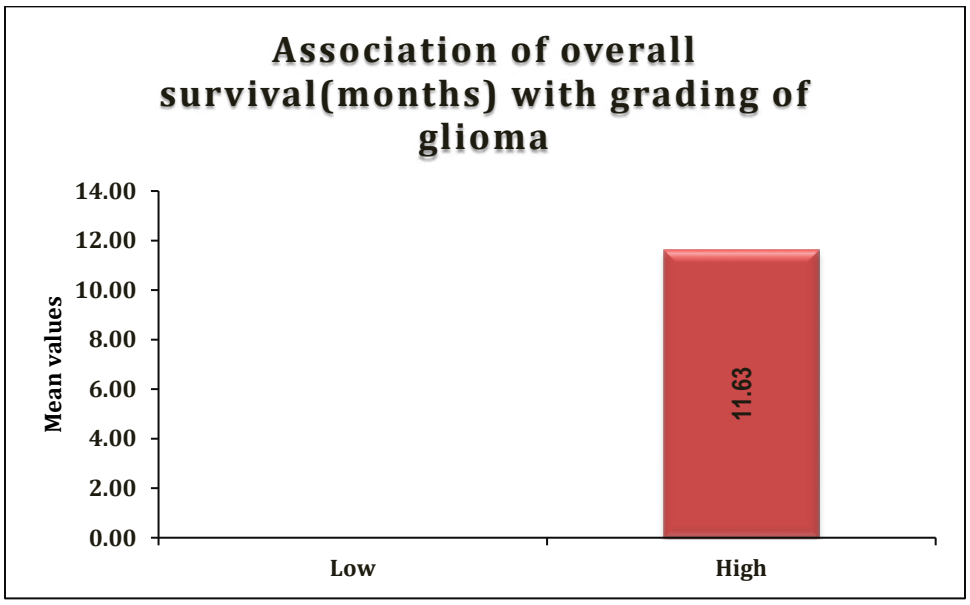

Figure 26.2:-Association of overall survival(months) with grading of glioma.

Compared to low grading group, high grading group had significantly lower proportion of alive patients (46.67% vs. 100%) and significantly higher proportion of died patients (53.33% vs. 0%) (p value = 0.0001). Mean ± SD of overall survival in high grading group was 11.62 ± 5.54 months with median (25th-75th percentile) of 14 (6.75-16) months. None of the patients with low grade glioma expired in this period of 2 years (Table 26, Figures 26.1 and 26.2).

Correlation of High Grade Gliomas with Immunohistochemical markers

a. IDH

Table 27:-Association of IDH status with grading of glioma.

IDH status	Low(n=15)	High(n=45)	Total	P value
Negative	4 (26.67%)	34 (75.56%)	38 (63.33%)	0.001*
Positive	11 (73.33%)	11 (24.44%)	22 (36.67%)	
Total	15 (100%)	45 (100%)	60 (100%)	

* **Fisher's exact test**

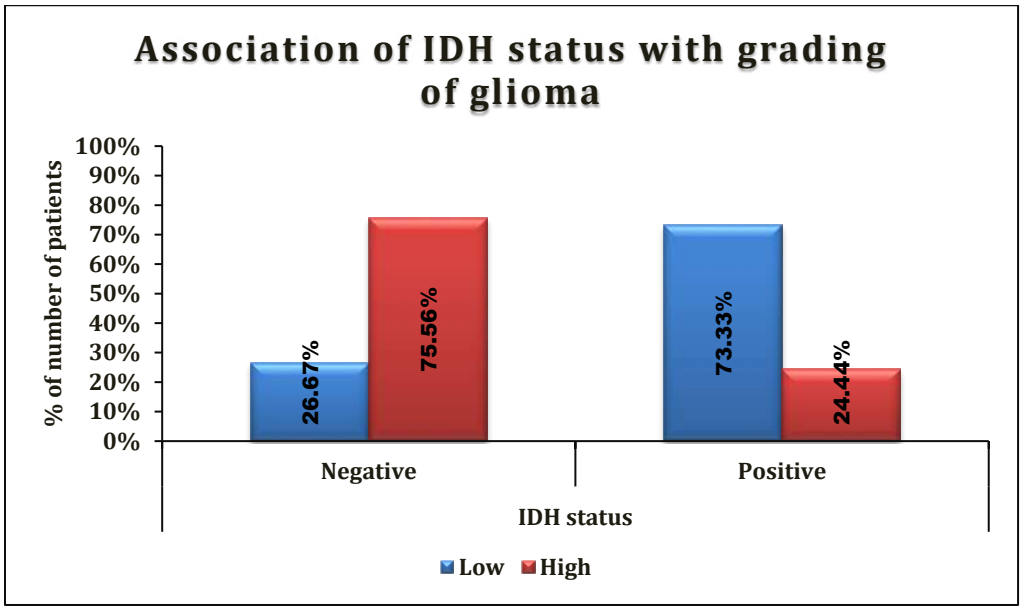

Figure 27:-Association of IDH status with grading of glioma.

Compared to low grading group, high grading group had lower proportion of patients with positive IDH status (24.44% vs. 73.33%) and higher proportion with negative IDH status (75.56% vs. 26.67%) (p value = 0.001) (Table 27, Figure 27).

b. ATRX

Table 28:-Association of ATRX status with grading of glioma.

ATRX status	Low(n=15)	High(n=45)	Total	P value
Retained nuclear expression	8 (53.33%)	36 (80%)	44 (73.33%)	0.043†
Loss of expression	7 (46.67%)	9 (20%)	16 (26.67%)	
Total	15 (100%)	45 (100%)	60 (100%)	

† **Chi square test**

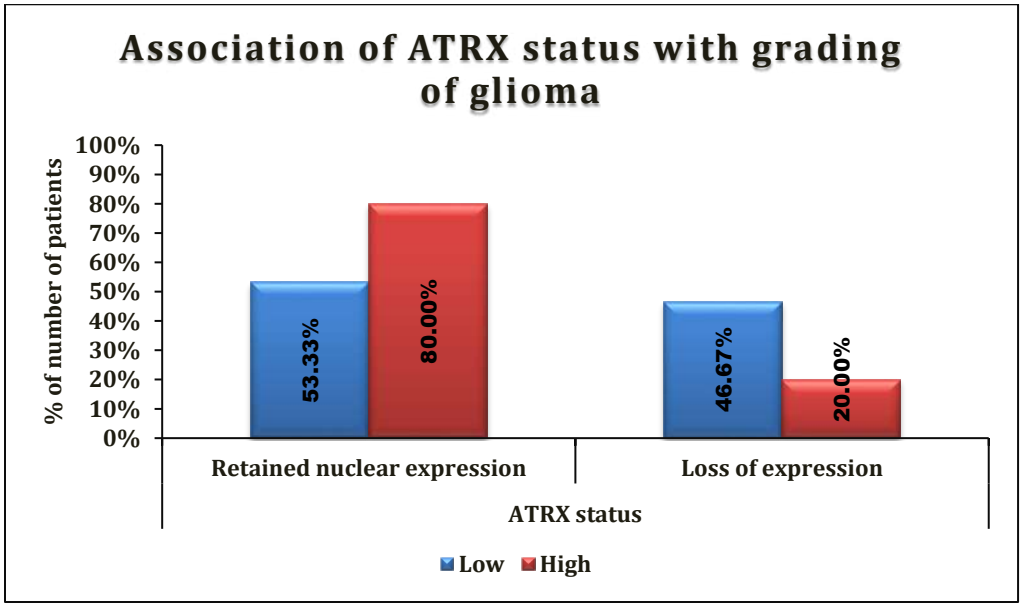

Figure 28:-Association of ATRX status with grading of glioma.

Compared to low grading group, high grading group had significantly lower proportion of patients with ATRX status showing loss of expression (20% vs. 46.67%) and significantly higher proportion with retained nuclear expression (80% vs. 53.33%) (p value = 0.043) (Table 28, Figure 28).

c. p53

Table 29:-Association of p53 status with grading of glioma.

P53 status	Low(n=15)	High(n=45)	Total	P value
Negative	7 (46.67%)	30 (66.67%)	37 (61.67%)	0.168†
Positive	8 (53.33%)	15 (33.33%)	23 (38.33%)	
Total	15 (100%)	45 (100%)	60 (100%)	

† **Chi square test**

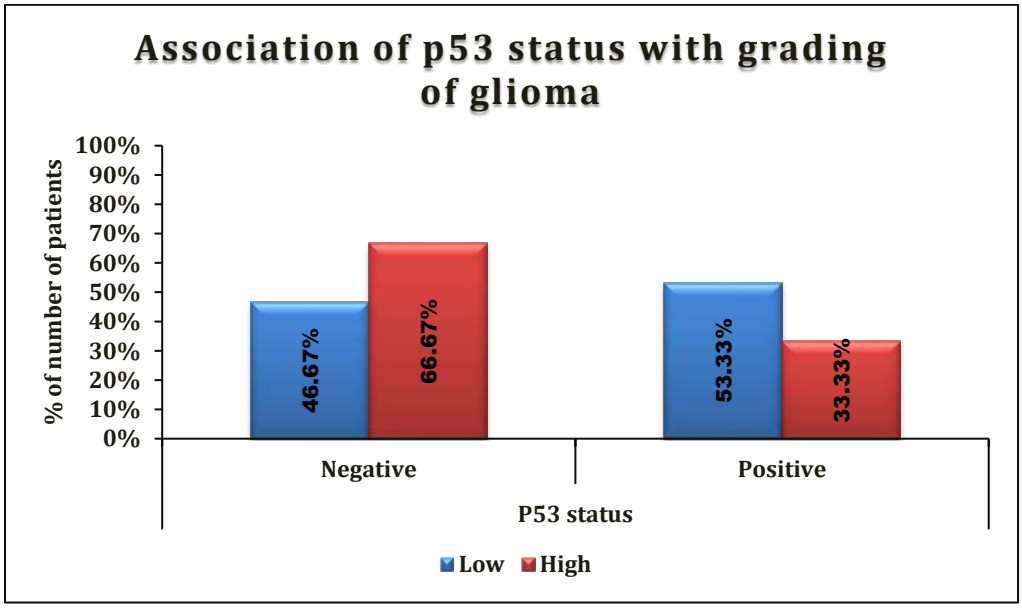

Figure 29:-Association of p53 status with grading of glioma.

Compared to low grading group, high grading group had comparable distribution of p53 status: negative status was 66.67% in high group vs. 46.67% in low group, while positive status was 33.33% vs. 53.33% respectively (p value = 0.168) (Table 29, Figure 29).

d. MIB index

Table 30:-Association of MIB index with grading of glioma.

MIB index	Low(n=15)	High(n=45)	Total	P value
0% to 5%	12 (80%)	6 (13.33%)	18 (30%)	<.0001*
>5% to 10%	3 (20%)	13 (28.89%)	16 (26.67%)	
>10% to 15%	0 (0%)	14 (31.11%)	14 (23.33%)	
>15% to 20%	0 (0%)	11 (24.44%)	11 (18.33%)	
>20%	0 (0%)	1 (2.22%)	1 (1.67%)	
Total	15 (100%)	45 (100%)	60 (100%)	

* **Fisher's exact test**

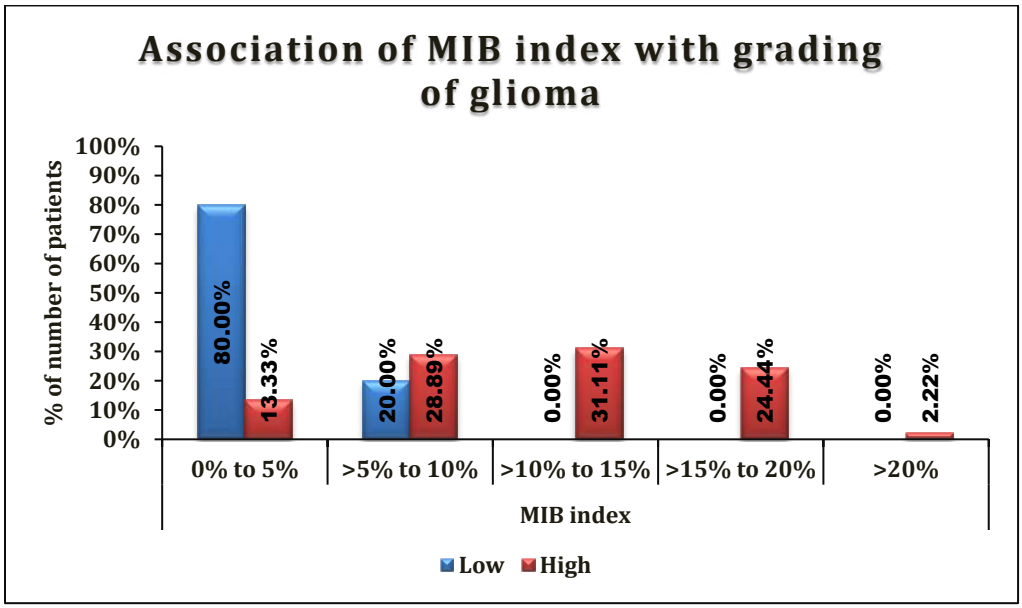

Figure 30:-Association of MIB index with grading of glioma.

Compared to low grading group, high grading group had significantly lower proportion of patients with MIB index of 0% to 5% (13.33% vs. 80%) and significantly higher proportions with MIB indices of >5% to 10% (28.89% vs. 20%), >10% to 15% (31.11% vs. 0%), >15% to 20% (24.44% vs. 0%) and >20% (2.22% vs. 0%) (p value < 0.0001) (Table 30, Figure 30).

e. Olig2

Table 31:-Association of olig2 with grading of glioma.

Olig2	Low(n=15)	High(n=45)	Total	P value
Negative	5 (33.33%)	32 (71.11%)	37 (61.67%)	0.009†
Positive	10 (66.67%)	13 (28.89%)	23 (38.33%)	
Total	15 (100%)	45 (100%)	60 (100%)	

† **Chi square test**

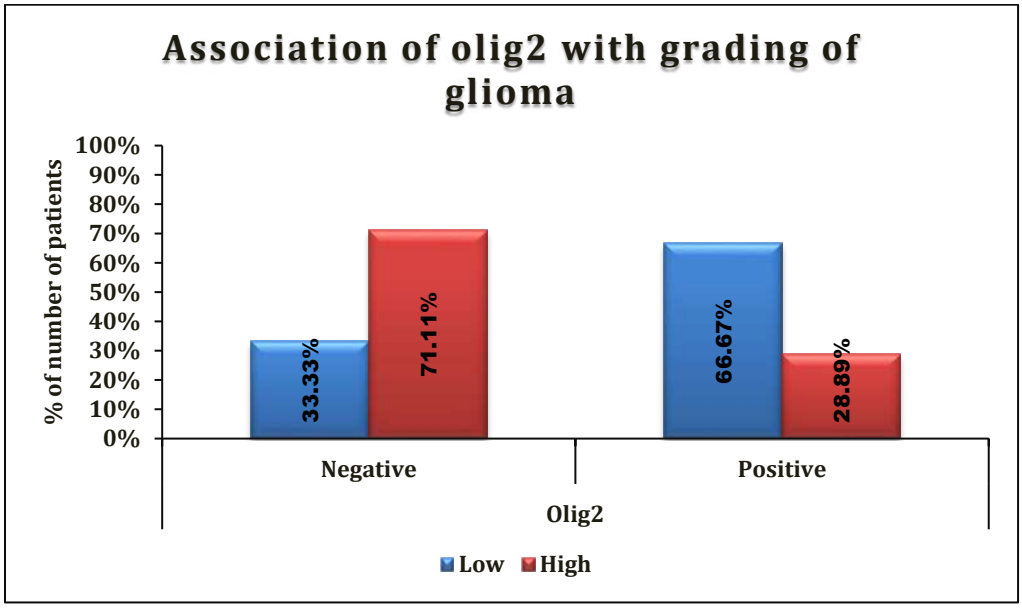

Figure 31:-Association of olig2 with grading of glioma.

Compared to low grading group, high grading group had significantly lower proportion of patients with positive olig2 status (28.89% vs. 66.67%) and significantly higher proportion with negative olig2 status (71.11% vs. 33.33%) (p value = 0.009) (Table 31, Figure 31).

f. GFAP

Table 32:-Association of GFAP with grading of glioma.

GFAP	Low(n=15)	High(n=45)	Total	P value
Negative	13 (86.67%)	38 (84.44%)	51 (85%)	1*
Positive	2 (13.33%)	7 (15.56%)	9 (15%)	
Total	15 (100%)	45 (100%)	60 (100%)	

* **Fisher's exact test**

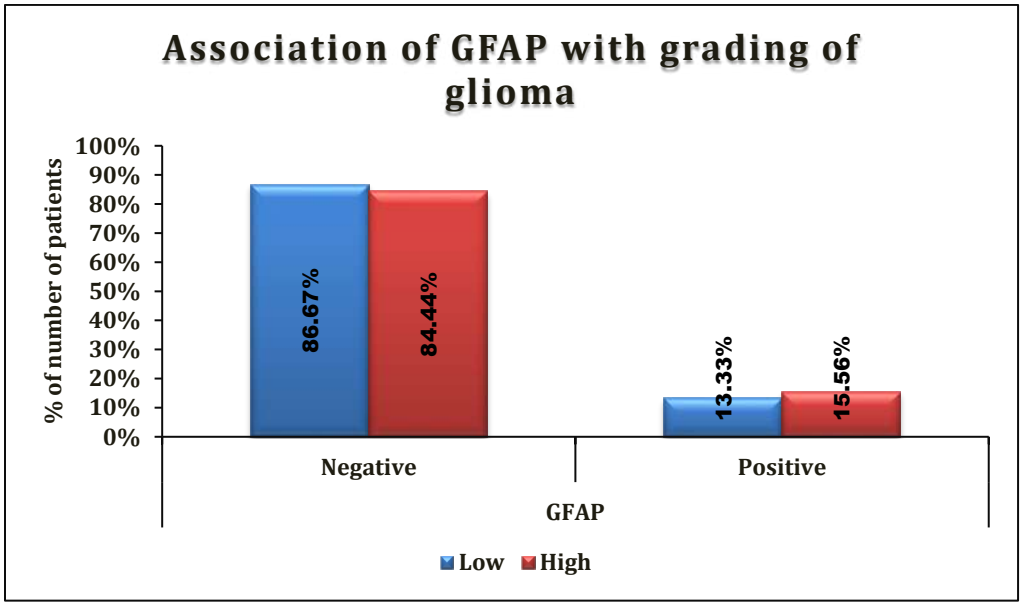

Figure 32:-Association of GFAP with grading of glioma.

Compared to low grading group, high grading group had comparable distribution of GFAP: negative status was 84.44% in high group vs. 86.67% in low group, while positive status was 15.56% vs. 13.33% respectively (p value = 1) (Table 32, Figure 32).

Correlation of High Grade Gliomas with Histopathological findings

Table 33:-Association of cellularity with grading of glioma.

Cellularity	Low(n=15)	High(n=45)	Total	P value
Low	4 (26.67%)	2 (4.44%)	6 (10%)	0.0007*
Moderate	8 (53.33%)	11 (24.44%)	19 (31.67%)	
High	3 (20%)	32 (71.11%)	35 (58.33%)	
Total	15 (100%)	45 (100%)	60 (100%)	

* **Fisher's exact test**

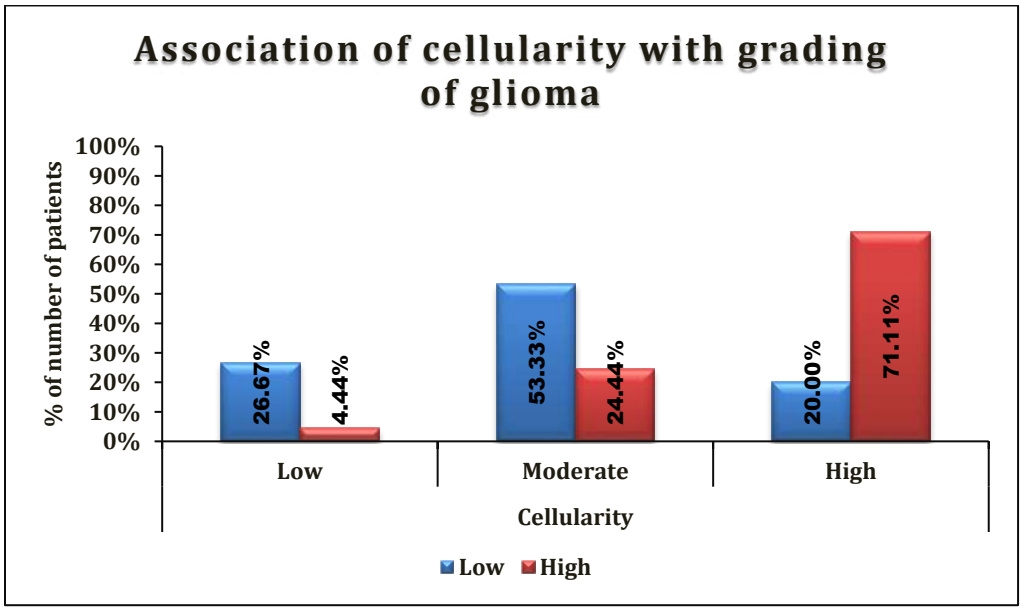

Figure 33:-Association of cellularity with grading of glioma.

Compared to low grading of glioma, high grading had significantly lower proportion of patients with low cellularity (4.44% vs. 26.67%) and moderate cellularity (24.44% vs. 53.33%). Conversely, proportion of patients with high cellularity was significantly higher in high grading compared to low grading (71.11% vs. 20%) (p value = 0.0007) (Table 33, Figure 33).

Table 34:-Association of mitotic activity with grading of glioma.

Mitotic activity	Low(n=15)	High(n=45)	Total	P value
Low	13 (86.67%)	8 (17.78%)	21 (35%)	<.0001*
High	2 (13.33%)	37 (82.22%)	39 (65%)	
Total	15 (100%)	45 (100%)	60 (100%)	

* **Fisher's exact test**

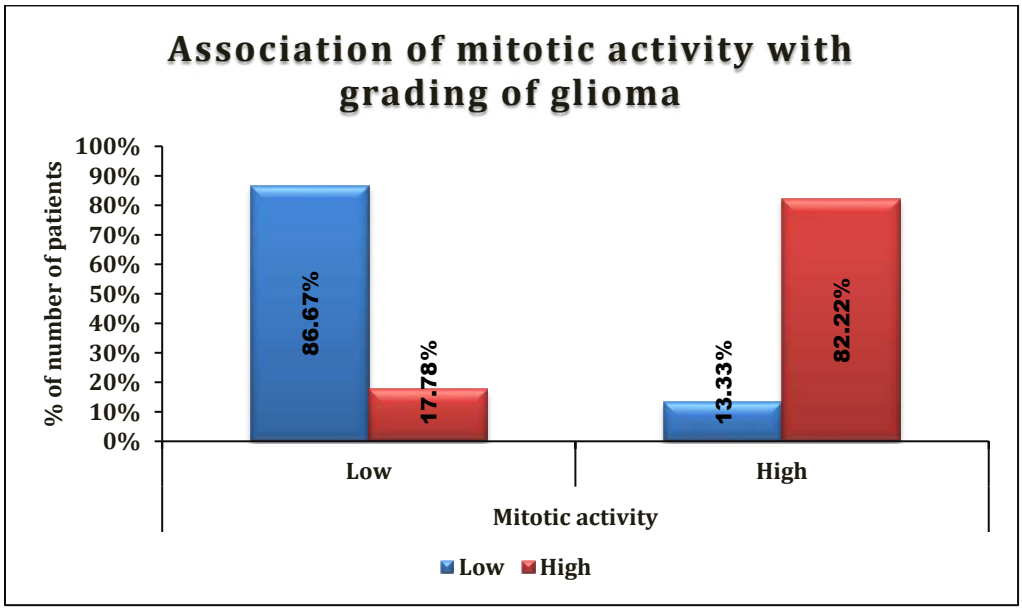

Figure 34:-Association of mitotic activity with grading of glioma.

Compared to low grading of glioma, high grading had significantly lower proportion of patients with low mitotic activity (17.78% vs. 86.67%). Conversely, proportion of patients with high mitotic activity was significantly higher in high grading compared to low grading (82.22% vs. 13.33%) (p value < 0.0001) (Table 34, Figure 34).

Table 35:-Association of nuclear atypia with grading of glioma.

Nuclear atypia	Low(n=15)	High(n=45)	Total	P value
Mild	5 (33.33%)	2 (4.44%)	7 (11.67%)	0.004*
Moderate	9 (60%)	27 (60%)	36 (60%)	
High	1 (6.67%)	16 (35.56%)	17 (28.33%)	
Total	15 (100%)	45 (100%)	60 (100%)	

* **Fisher's exact test**

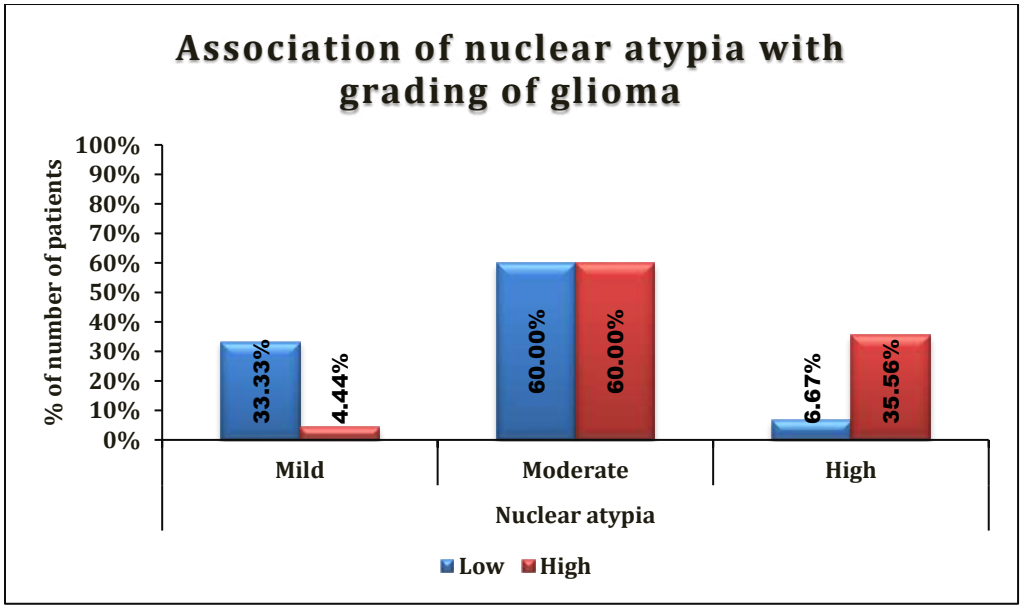

Figure 35:-Association of nuclear atypia with grading of glioma.

Compared to low grading of glioma, high grading had significantly lower proportion of mild nuclear atypia (4.44% vs. 33.33%) and significantly higher proportion of high nuclear atypia (35.56% vs. 6.67%), while moderate nuclear atypia was similar in both groups (60%) (p value = 0.004) (Table 35, Figure 35).

Table 36:-Association of microvascular proliferation with grading of glioma.

Microvascular proliferation	Low(n=15)	High(n=45)	Total	P value
Absent	13 (86.67%)	14 (31.11%)	27 (45%)	0.0002*
Present	2 (13.33%)	31 (68.89%)	33 (55%)	
Total	15 (100%)	45 (100%)	60 (100%)	

* **Fisher's exact test**

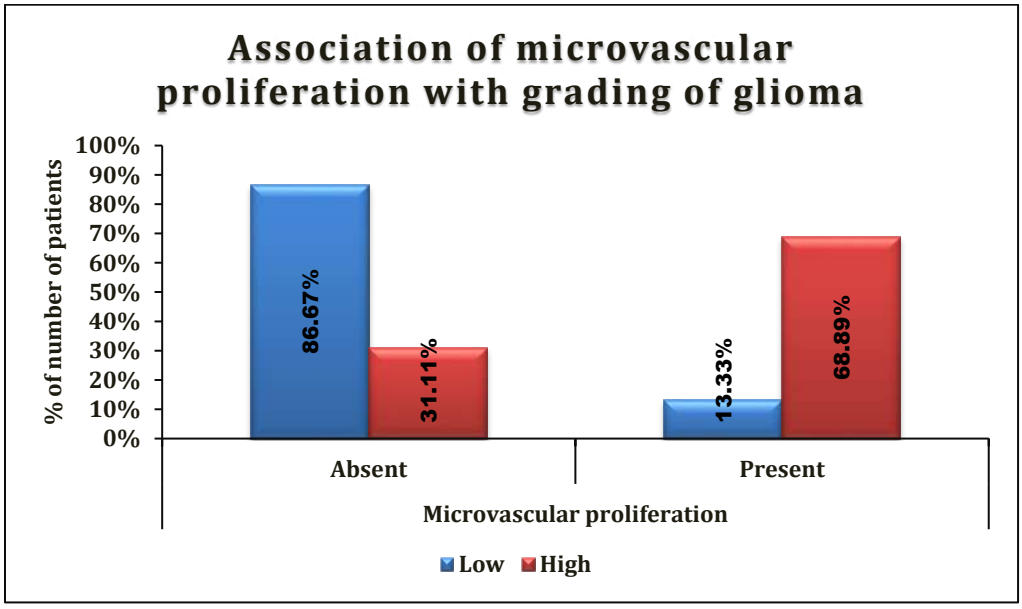

Figure 36:-Association of microvascular proliferation with grading of glioma.

Compared to low grading of glioma, high grading had significantly lower proportion of patients without microvascular proliferation (31.11% vs. 86.67%) and significantly higher proportion with microvascular proliferation (68.89% vs. 13.33%) (p value = 0.0002) (Table 36, Figure 36).

Table 37:-Association of necrosis with grading of glioma.

Necrosis	Low(n=15)	High(n=45)	Total	P value
Absent	14 (93.33%)	13 (28.89%)	27 (45%)	<.0001*
Present	1 (6.67%)	32 (71.11%)	33 (55%)	
Total	15 (100%)	45 (100%)	60 (100%)	

* **Fisher's exact test**

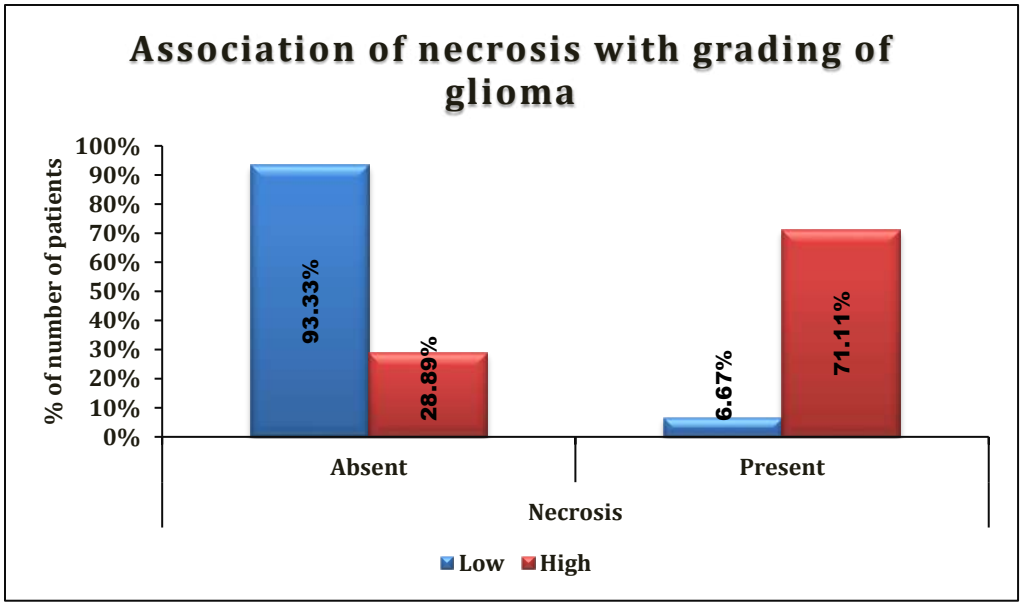

Figure 37:-Association of necrosis with grading of glioma.

Compared to low grading of glioma, high grading had significantly lower proportion of patients without necrosis (28.89% vs. 93.33%) and significantly higher proportion with necrosis (71.11% vs. 6.67%) (p value < 0.0001) (Table 37, Figure 37).

Table 38:-Association of grading of glioma with type of tumor.

Grading of glioma	Glioblastoma(n=24)	Astrocytoma(n=11)	Oligodendroglioma(n=10)	Pilocytic astrocytoma(n=3)	Oligoastrocytoma(n=2)	Anaplastic oligodendroglioma(n=2)	Diffuse adult glioma (n=2)	Diffuse astrocytic glioma (n=2)	Diffuse midline glioma (n=1)	Ependymoma(n=1)	Ganglioglioma(n=1)	Low grade glioma NOS(n=1)	Total	P value
Low	0 (0%)	6 (54.55%)	4 (40%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)	15 (25%)	
High	24 (100%)	5 (45.45%)	6 (60%)	0 (0%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	45 (75%)	<.0001*
Total	24 (100%)	11 (100%)	10 (100%)	3 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	60 (100%)	

* **Fisher's exact test**

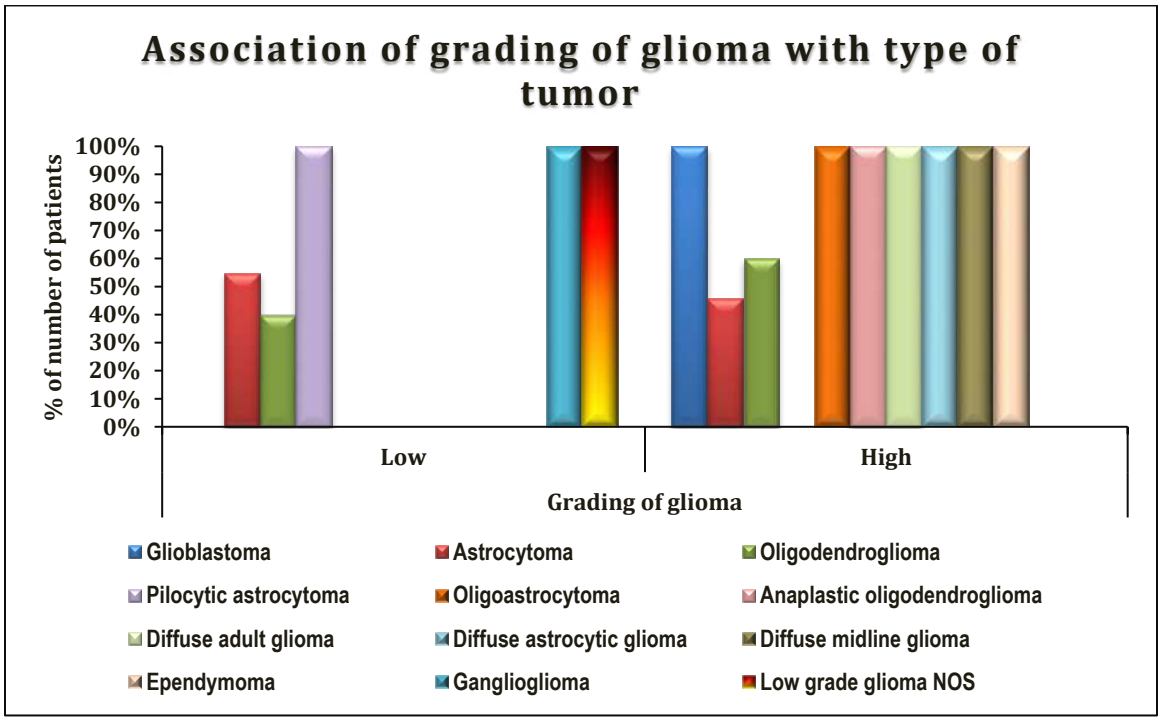

Figure 38- Grade of glioma and tumor typ.

Low grade tumors identified in the study were pilocytic astrocytoma, ganglioglioma and low grade glioma NOS. High grade tumors identified in this study were glioblastoma, oligoastrocytoma, anaplastic oligodendroglioma, diffuse adult glioma, diffuse astrocytic glioma, diffuse midline glioma and ependymoma. Astrocytomas and oligodenrogliomas had both high grade and low grade tumor types.(Table 38, Figure 38).

Clinical evolution of IDH positive tumors

Table 39:-Association of age with IDH status.

Age	Negative(n=38)	Positive(n=22)	Total	P value
10 to 20 years	4 (10.53%)	1 (4.55%)	5 (8.33%)	0.131*
21 to 30 years	5 (13.16%)	7 (31.82%)	12 (20%)	
31 to 40 years	7 (18.42%)	8 (36.36%)	15 (25%)	
41 to 50 years	9 (23.68%)	4 (18.18%)	13 (21.67%)	
51 to 60 years	9 (23.68%)	2 (9.09%)	11 (18.33%)	
61 to 70 years	4 (10.53%)	0 (0%)	4 (6.67%)	
Mean ± SD	42.05 ± 15.37	34.95 ± 10.52	39.45 ± 14.12	0.06‡
Median(25th-75th percentile)	42(33.5-52)	35(30-41.5)	39.5(30-50.25)	
Range	10-70	14-56	10-70	

‡ **Independent t test,** * **Fisher's exact test**

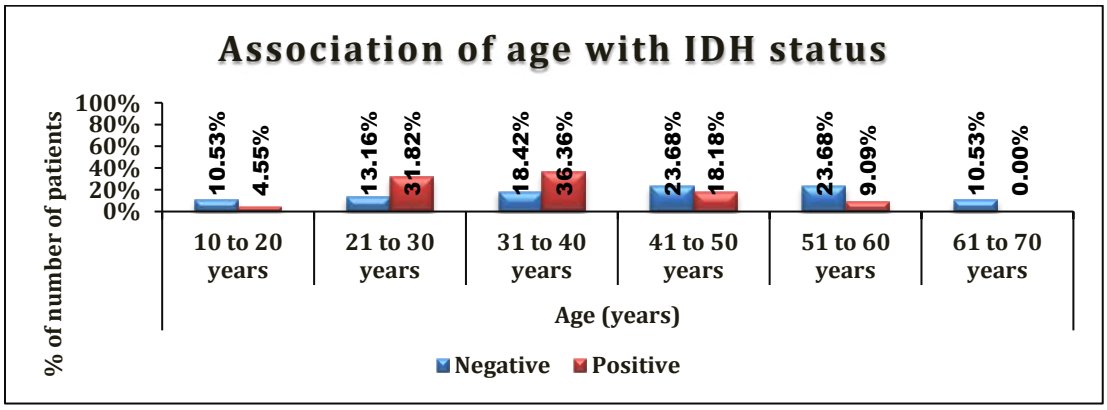

Figure 39:-Association of age with IDH status.

Compared to negative IDH status, positive IDH status had comparable distribution of age: 4.55% of patients in positive group were 10 to 20 years old vs. 10.53% in negative group, 31.82% vs. 13.16% were 21 to 30 years, 36.36% vs. 18.42% were 31 to 40 years, 18.18% vs. 23.68% were 41 to 50 years, 9.09% vs. 23.68% were 51 to 60 years and 0% vs. 10.53% were 61 to 70 years (p value = 0.131). Mean ± SD age was 34.95 ± 10.52 years in positive group vs. 42.05 ± 15.37 years in negative group, with no significant association between them (p value = 0.06) (Table 39, Figure 39).

Table 40:-Association of gender with IDH status.

Gender	Negative(n=38)	Positive(n=22)	Total	P value
Female	11 (28.95%)	5 (22.73%)	16 (26.67%)	0.6†
Male	27 (71.05%)	17 (77.27%)	44 (73.33%)	
Total	38 (100%)	22 (100%)	60 (100%)	

† **Chi square test**

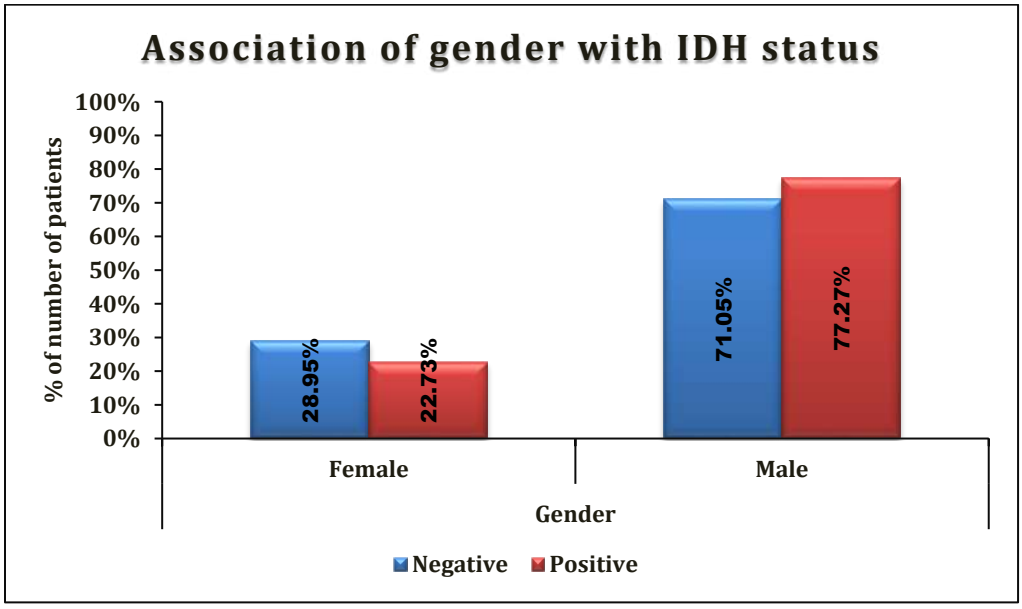

Figure 40:-Association of gender with IDH status.

Compared to negative IDH status, positive IDH status had comparable distribution of gender: females were 22.73% in positive group vs. 28.95% in negative group and males were 77.27% vs. 71.05%, respectively (p value = 0.6) (Table 40, Figure 40).

Table 41:-Association of clinical symptomatology with IDH status.

Clinical symptomatology	Negative(n=38)	Positive(n=22)	Total	P value
Seizures	14 (36.84%)	10 (45.45%)	24 (40%)	0.792*
Headache	9 (23.68%)	4 (18.18%)	13 (21.67%)	
Motor weakness	7 (18.42%)	6 (27.27%)	13 (21.67%)	
Visual disturbance	7 (18.42%)	2 (9.09%)	9 (15%)	
Aphasia and dementia	1 (2.63%)	0 (0%)	1 (1.67%)	
Total	38 (100%)	22 (100%)	60 (100%)	

* **Fisher's exact test**

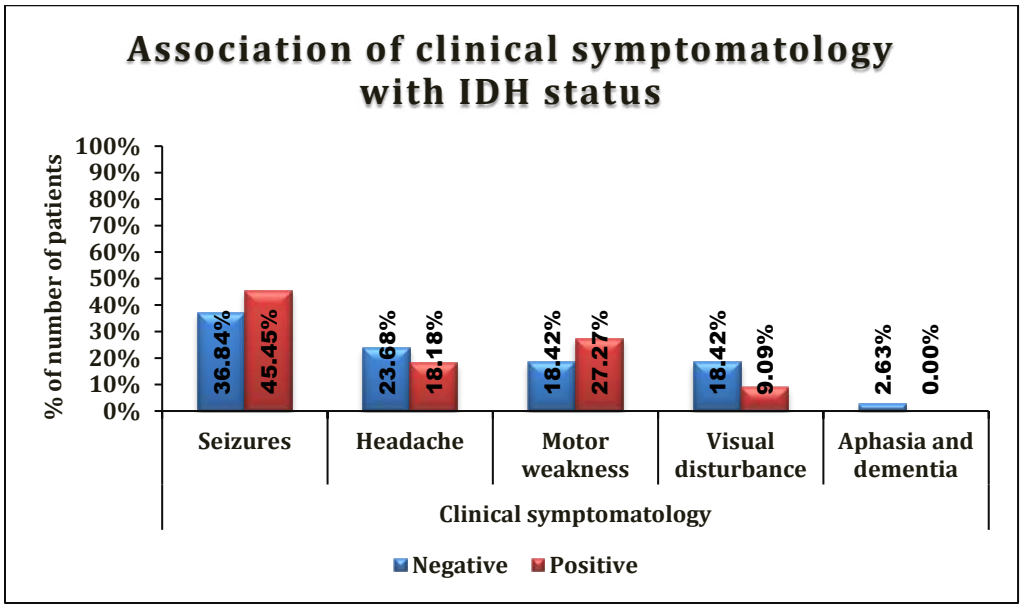

Figure 41:-Association of clinical symptomatology with IDH status.

Compared to negative IDH status, positive IDH status had comparable distribution of clinical symptomatology: seizures were 45.45% in positive group vs. 36.84% in negative group, headache was 18.18% vs. 23.68%, motor weakness was 27.27% vs. 18.42%, visual disturbance was 9.09% vs. 18.42% and aphasia and dementia was 0% vs. 2.63% (p value = 0.792) (Table 41, Figure 41).

Table 42:-Association of neurological deficit with IDH status.

Neurological deficit	Negative(n=38)	Positive(n=22)	Total	P value
Absent	12 (31.58%)	11 (50%)	23 (38.33%)	0.157†
Present	26 (68.42%)	11 (50%)	37 (61.67%)	
Total	38 (100%)	22 (100%)	60 (100%)	

† **Chi square test**

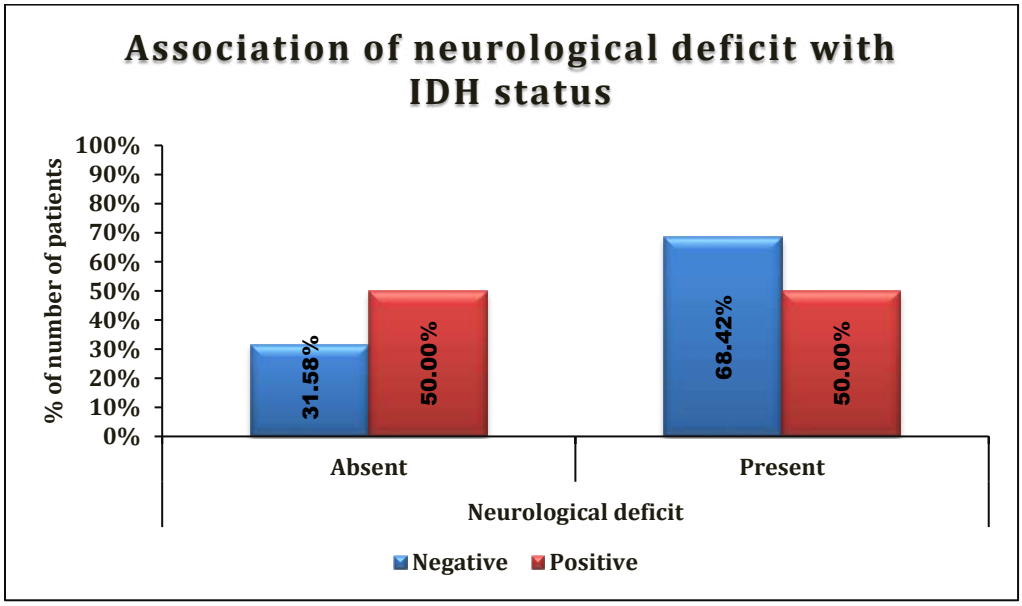

Figure 42:-Association of neurological deficit with IDH status.

Compared to negative IDH status, positive IDH status had comparable distribution of neurological deficit: absence of deficit was 50% in positive group vs. 31.58% in negative group and presence of deficit was 50% vs. 68.42% respectively (p value = 0.157) (Table 42, Figure 42).

Table 43:-Association of region with IDH status.

Region	Negative(n=38)	Positive(n=22)	Total	P value
Lateral brain	33 (86.84%)	20 (90.91%)	53 (88.33%)	0.832*
Midline	3 (7.89%)	2 (9.09%)	5 (8.33%)	
Thalamic	2 (5.26%)	0 (0%)	2 (3.33%)	
Total	38 (100%)	22 (100%)	60 (100%)	

* **Fisher's exact test**

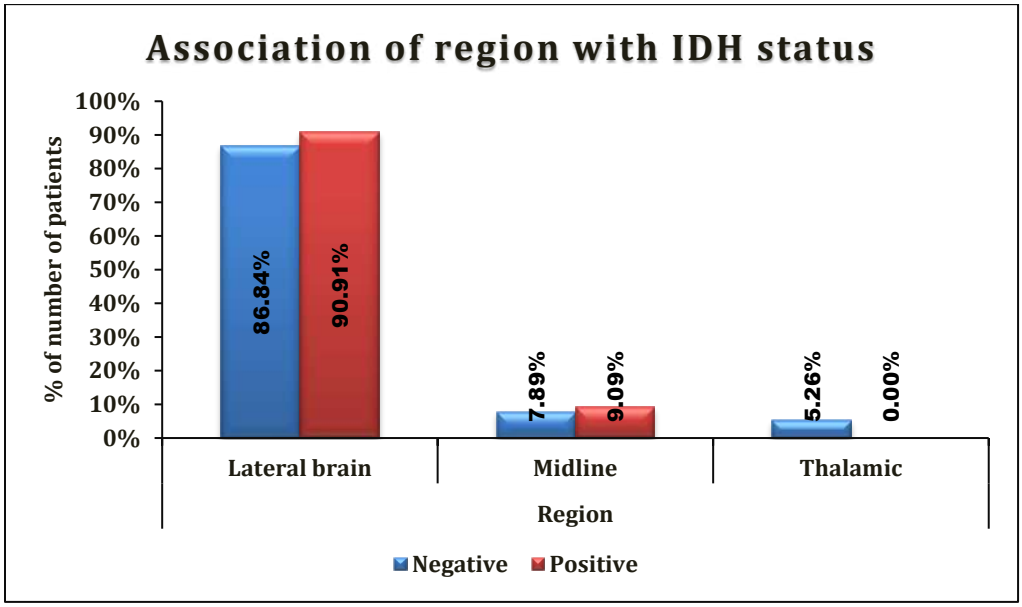

Figure 43:-Association of region with IDH status.

Compared to negative IDH status, positive IDH status had comparable distribution of region: lateral brain involvement was 90.91% in positive group vs. 86.84% in negative group, midline involvement was 9.09% vs. 7.89% and thalamic involvement was 0% vs. 5.26% (p value = 0.832) (Table 43, Figure 43).

Table 44:-Association of WHO grade with IDH status.

WHO grade	Negative(n=38)	Positive(n=22)	Total	P value
Grade I	4 (10.53%)	1 (4.55%)	5 (8.33%)	<.0001*
Grade II	4 (10.53%)	10 (45.45%)	14 (23.33%)	
Grade III	4 (10.53%)	9 (40.91%)	13 (21.67%)	
Grade IV	26 (68.42%)	2 (9.09%)	28 (46.67%)	
Total	38 (100%)	22 (100%)	60 (100%)	

* **Fisher's exact test**

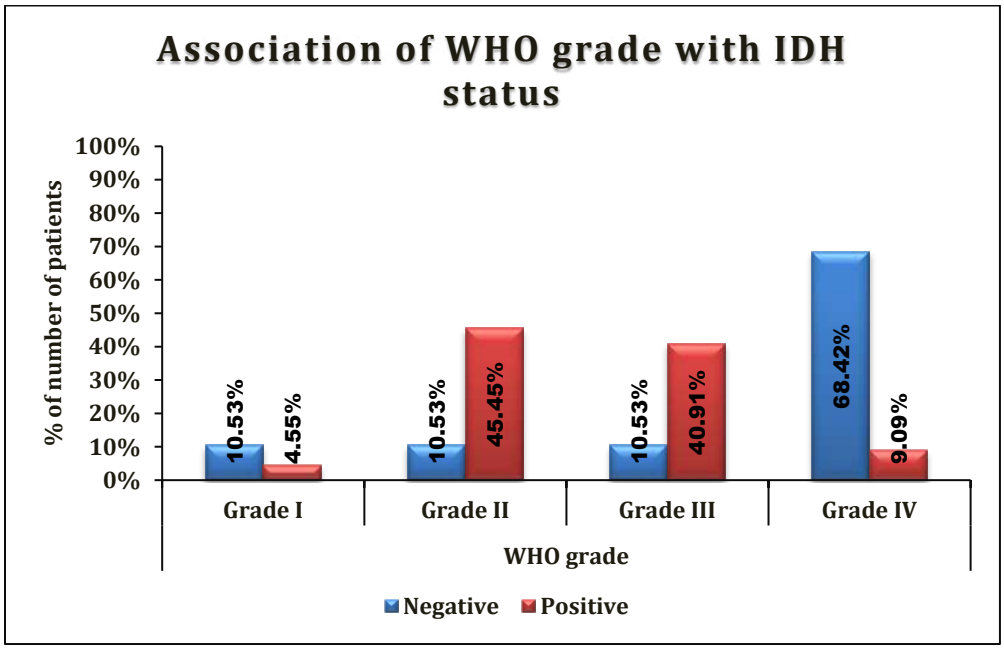

Figure 44:-Association of WHO grade with IDH status.

Compared to negative IDH status, positive IDH status had significantly lower proportion of patients with WHO grade I (4.55% vs. 10.53%) and grade IV (9.09% vs. 68.42%). Conversely, proportion of patients with WHO grade II (45.45% vs. 10.53%) and grade III (40.91% vs. 10.53%) was significantly higher in positive IDH status compared to negative (p value < 0.0001) (Table 44, Figure 44).

Table 45:-Association of ATRX status with IDH status.

ATRX status	Negative(n=38)	Positive(n=22)	Total	P value
Retained nuclear expression	31 (81.58%)	13 (59.09%)	44 (73.33%)	0.058†
Loss of expression	7 (18.42%)	9 (40.91%)	16 (26.67%)	
Total	38 (100%)	22 (100%)	60 (100%)	

† **Chi square test**

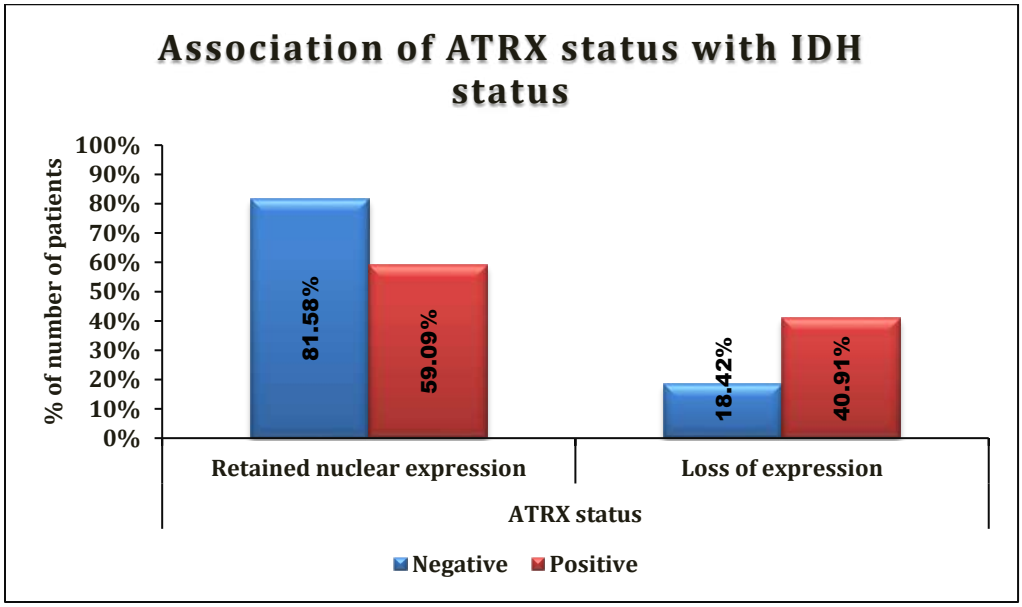

Figure 45:-Association of ATRX status with IDH status.

Compared to negative IDH status, positive IDH status had comparable distribution of ATRX status: retained nuclear expression was 59.09% in positive group vs. 81.58% in negative group, while loss of expression was 40.91% vs. 18.42% (p value = 0.058) (Table 45, Figure 45).

Table 46:-Association of p53 status with IDH status.

P53 status	Negative(n=38)	Positive(n=22)	Total	P value
Negative	26 (68.42%)	11 (50%)	37 (61.67%)	0.157†
Positive	12 (31.58%)	11 (50%)	23 (38.33%)	
Total	38 (100%)	22 (100%)	60 (100%)	

† **Chi square test**

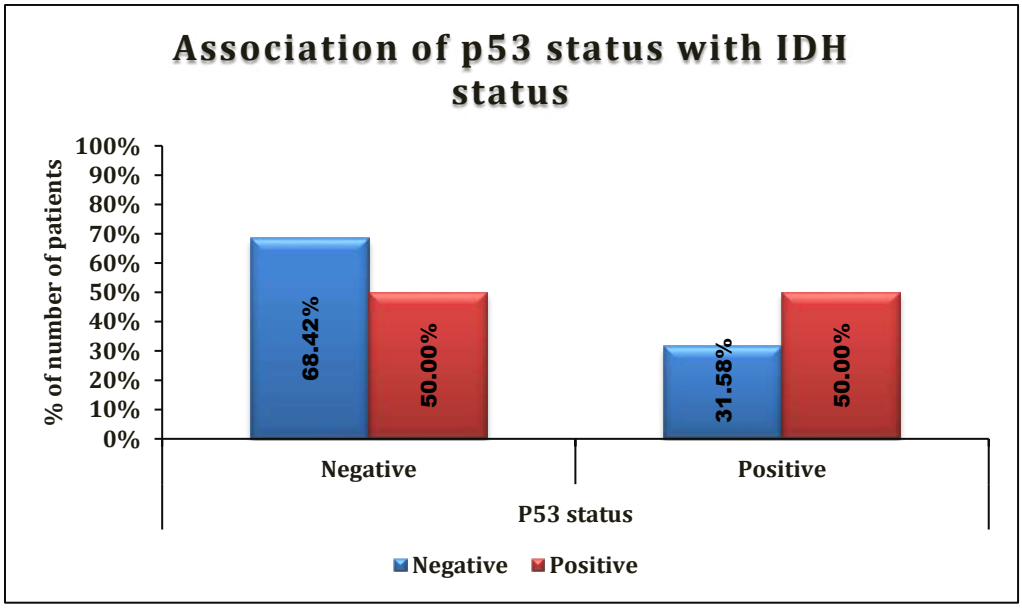

Figure 46:-Association of p53 status with IDH status.

Compared to negative IDH status, positive IDH status had comparable distribution of p53 status: negative p53 status was 50% in positive IDH status group vs. 68.42% in negative IDH status group, while positive p53 status was 50% vs. 31.58% (p value = 0.157) (Table 46, Figure 46).

Table 47:-Association of MIB1 index with IDH status.

MIB1 index	Negative(n=38)	Positive(n=22)	Total	P value
0% to 5%	10 (26.32%)	8 (36.36%)	18 (30%)	0.364*
>5% to 10%	8 (21.05%)	8 (36.36%)	16 (26.67%)	
>10% to 15%	10 (26.32%)	4 (18.18%)	14 (23.33%)	
>15% to 20%	9 (23.68%)	2 (9.09%)	11 (18.33%)	
>20%	1 (2.63%)	0 (0%)	1 (1.67%)	
Total	38 (100%)	22 (100%)	60 (100%)	

* **Fisher's exact test**

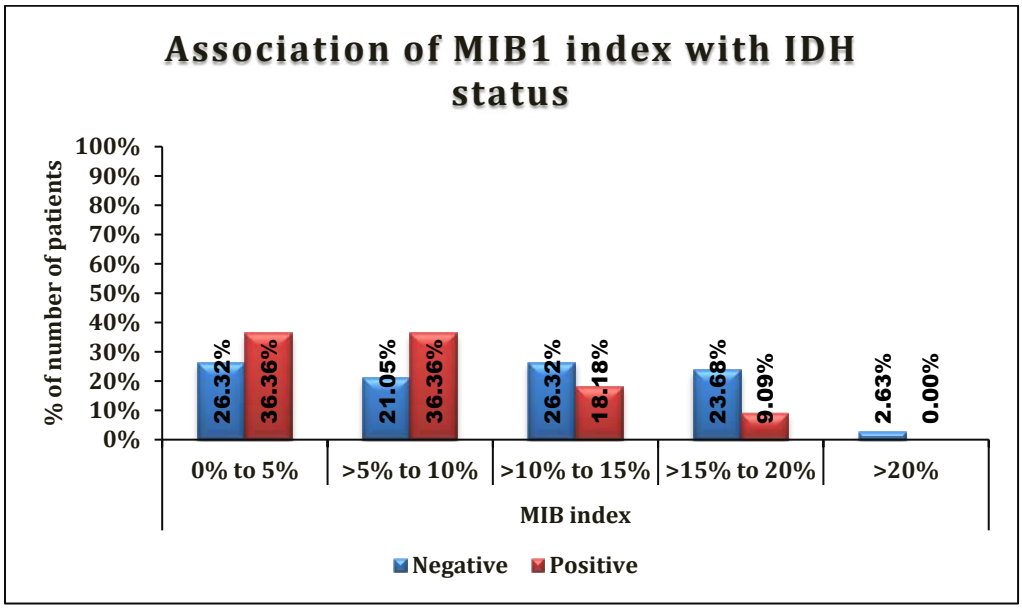

Figure 47:-Association of MIB1 index with IDH status.

Compared to negative IDH status, positive IDH status had comparable distribution of MIB index: 0% to 5% was 36.36% in positive group vs. 26.32% in negative group, >5% to 10% was 36.36% vs. 21.05%, >10% to 15% was 18.18% vs. 26.32%, >15% to 20% was 9.09% vs. 23.68% and >20% was 0% vs. 2.63% (p value = 0.364) (Table 47, Figure 47).

Table 48:-Association of olig2 with IDH status.

Olig2	Negative(n=38)	Positive(n=22)	Total	P value
Negative	25 (65.79%)	12 (54.55%)	37 (61.67%)	0.388†
Positive	13 (34.21%)	10 (45.45%)	23 (38.33%)	
Total	38 (100%)	22 (100%)	60 (100%)	

† **Chi square test**

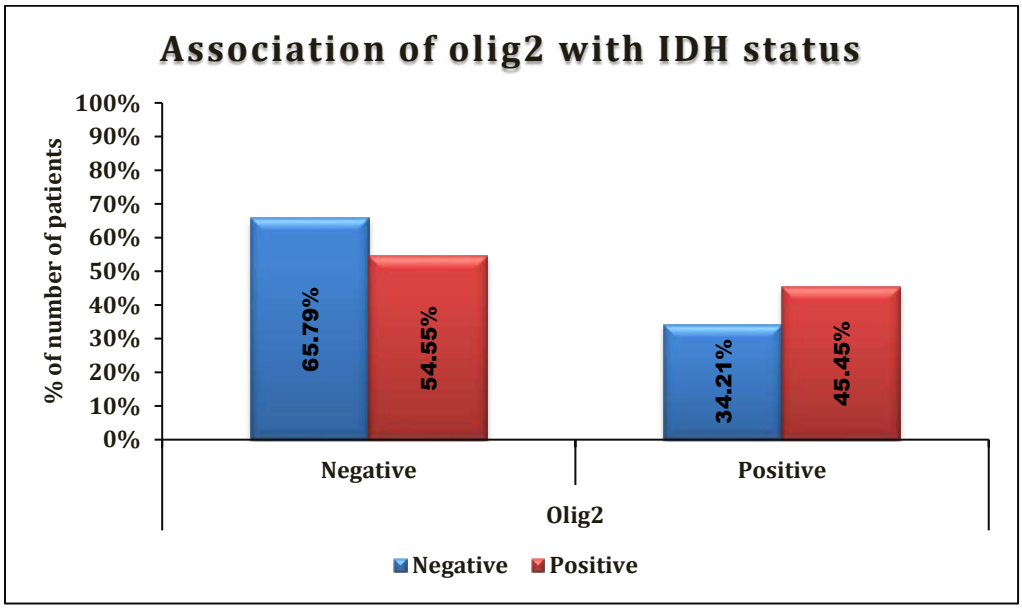

Figure 48:-Association of olig2 with IDH status.

Compared to negative IDH status, positive IDH status had comparable distribution of olig2: negative olig2 status was 54.55% in positive group vs. 65.79% in negative group, while positive olig2 status was 45.45% vs. 34.21% (p value = 0.388) (Table 48, Figure 48).

Table 49:-Association of GFAP with IDH status.

GFAP	Negative(n=38)	Positive(n=22)	Total	P value
Negative	29 (76.32%)	22 (100%)	51 (85%)	0.02*
Positive	9 (23.68%)	0 (0%)	9 (15%)	
Total	38 (100%)	22 (100%)	60 (100%)	

* **Fisher's exact test**

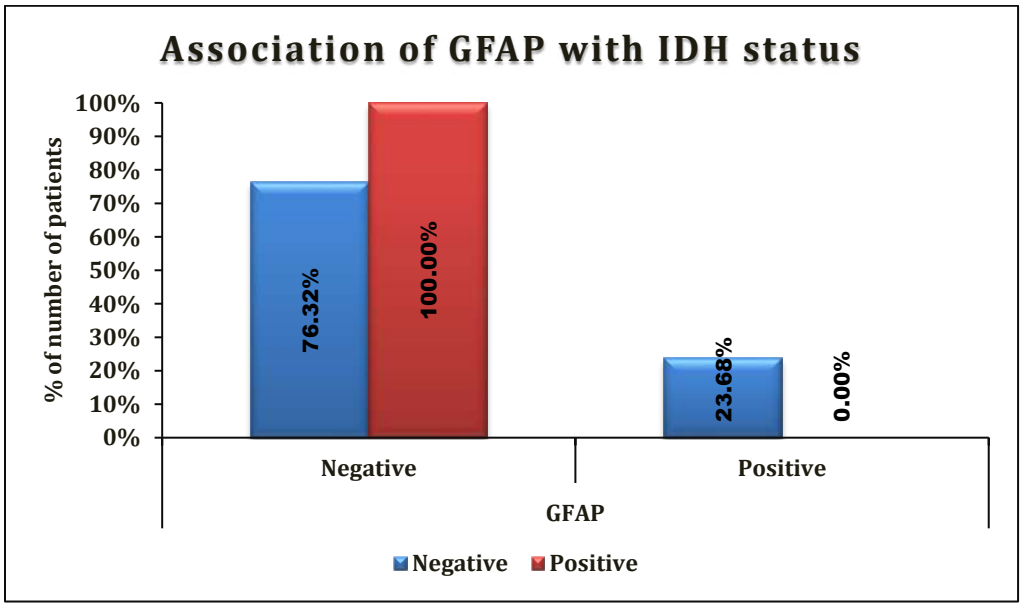

Figure 49:-Association of GFAP with IDH status.

Compared to negative IDH status, positive IDH status had significantly lower proportion of patients with positive GFAP (0% vs. 23.68%) and significantly higher proportion with negative GFAP (100% vs. 76.32%) (p value = 0.02) (Table 49, Figure 49).

Table 50:-Association of KPS and ECOG with IDH status.

KPS and ECOG	Negative	Positive	Total	P value
ECOG at 6 months				
0	3 (8.82%)	13 (61.90%)	16 (29.09%)	0.0002*
1	16 (47.06%)	7 (33.33%)	23 (41.82%)	
2	9 (26.47%)	1 (4.76%)	10 (18.18%)	
3	2 (5.88%)	0 (0%)	2 (3.64%)	
4	4 (11.76%)	0 (0%)	4 (7.27%)	
ECOG at 1year				
0	3 (10%)	9 (42.86%)	12 (23.53%)	0.002*
1	11 (36.67%)	9 (42.86%)	20 (39.22%)	
2	3 (10%)	3 (14.29%)	6 (11.76%)	
3	4 (13.33%)	0 (0%)	4 (7.84%)	
4	9 (30%)	0 (0%)	9 (17.65%)	
KPS at 6 months				
Mean ± SD	71.18 ± 25.32	92.38 ± 9.95	79.27 ± 23.16	<.0001‡
Median(25th-75th percentile)	80(52.5-97.5)	100(80-100)	80(60-100)	
Range	10-100	70-100	10-100	
KPS at 1year				
Mean ± SD	61 ± 33.87	86.67 ± 14.26	71.57 ± 30.16	0.0006‡
Median(25th-75th percentile)	60(25-97.5)	90(80-100)	80(50-100)	
Range	10-100	60-100	10-100	

‡ Independent t test, * Fisher's exact test

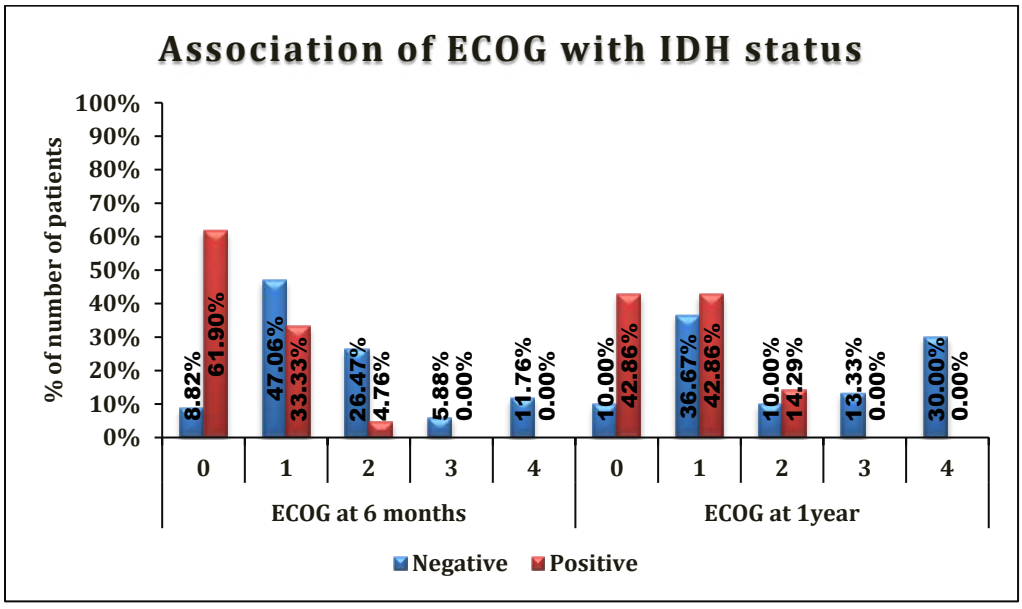

Figure 50.1:-Association of ECOG with IDH status.

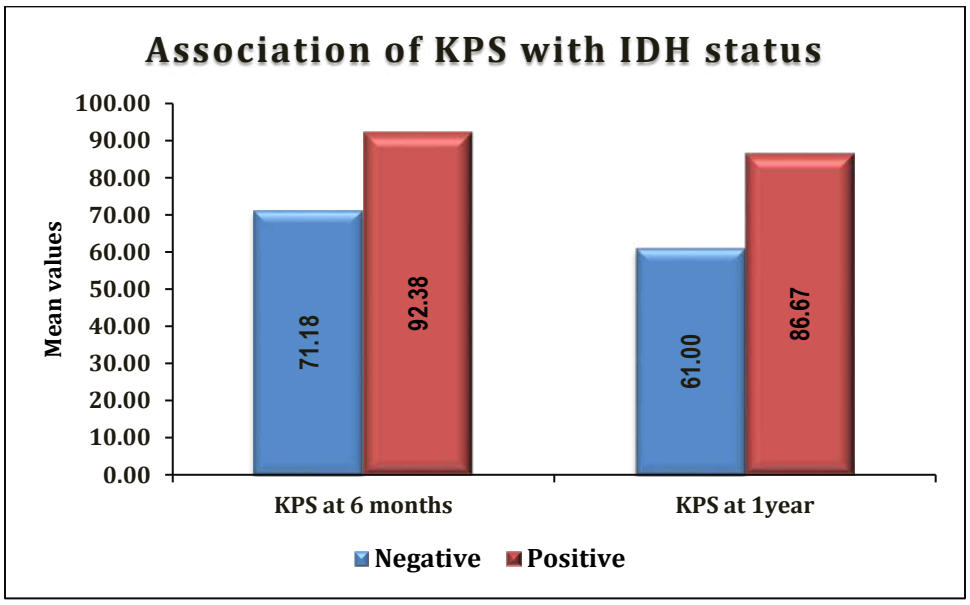

Figure 50.2:-Association of KPS with IDH status.

Compared to negative IDH status, positive IDH status had significantly lower proportion of patients with ECOG at 6 months of 1 (33.33% vs. 47.06%), 2 (4.76% vs. 26.47%), 3 (0% vs. 5.88%) and 4 (0% vs. 11.76%). Conversely, proportion of patients with ECOG at 6 months of 0 was significantly higher in positive IDH status compared to negative (61.90% vs. 8.82%) (p value = 0.0002).

At 1 year, positive IDH status had significantly lower proportion of patients with ECOG of 3 (0% vs. 13.33%) and 4 (0% vs. 30%). In contrast, proportion of patients with ECOG of 0 (42.86% vs. 10%), 1 (42.86% vs. 36.67%) and 2 (14.29% vs. 10%) was significantly higher in positive IDH status compared to negative IDH status (p value = 0.002).

Significant association was observed in KPS at 6 months and KPS at 1 year with IDH status (p value < 0.05). Mean ± SD of KPS at 6 months and KPS at 1 year in positive IDH status was 92.38 ± 9.95 and 86.67 ± 14.26 respectively, which was significantly higher compared to negative IDH status (71.18 ± 25.32, p value < 0.0001; 61 ± 33.87, p value = 0.0006) (Table 50, Figures 51.1 and 51.2).

Table 51:-Association of symptoms at 1 year with IDH status.

Symptoms at 1 year	Negative(n=30)	Positive(n=21)	Total	P value
BFU(Future uncertainty)	17 (56.67%)	6 (28.57%)	23 (45.10%)	0.047†
BVD (Visual disorder)	10 (33.33%)	4 (19.05%)	14 (27.45%)	0.346*
BMD(Motor deficit)	21 (70%)	5 (23.81%)	26 (50.98%)	0.001†
BCD(Communication deficit)	16 (53.33%)	2 (9.52%)	18 (35.29%)	0.002*
BHA(Headaches)	7 (23.33%)	6 (28.57%)	13 (25.49%)	0.673†
BSE(Seizures)	3 (10%)	1 (4.76%)	4 (7.84%)	0.634*
BDR(Drowsiness)	14 (46.67%)	4 (19.05%)	18 (35.29%)	0.073*
BBC (Loss of bladder control)	12 (40%)	1 (4.76%)	13 (25.49%)	0.007*
BHL (Hair loss)	17 (56.67%)	1 (4.76%)	18 (35.29%)	0.0001*
BWL (Weakness in lower limbs)	26 (86.67%)	10 (47.62%)	36 (70.59%)	0.004*
BIS (Itchy skin)	12 (40%)	1 (4.76%)	13 (25.49%)	0.007*

* **Fisher's exact test,** † **Chi square test**

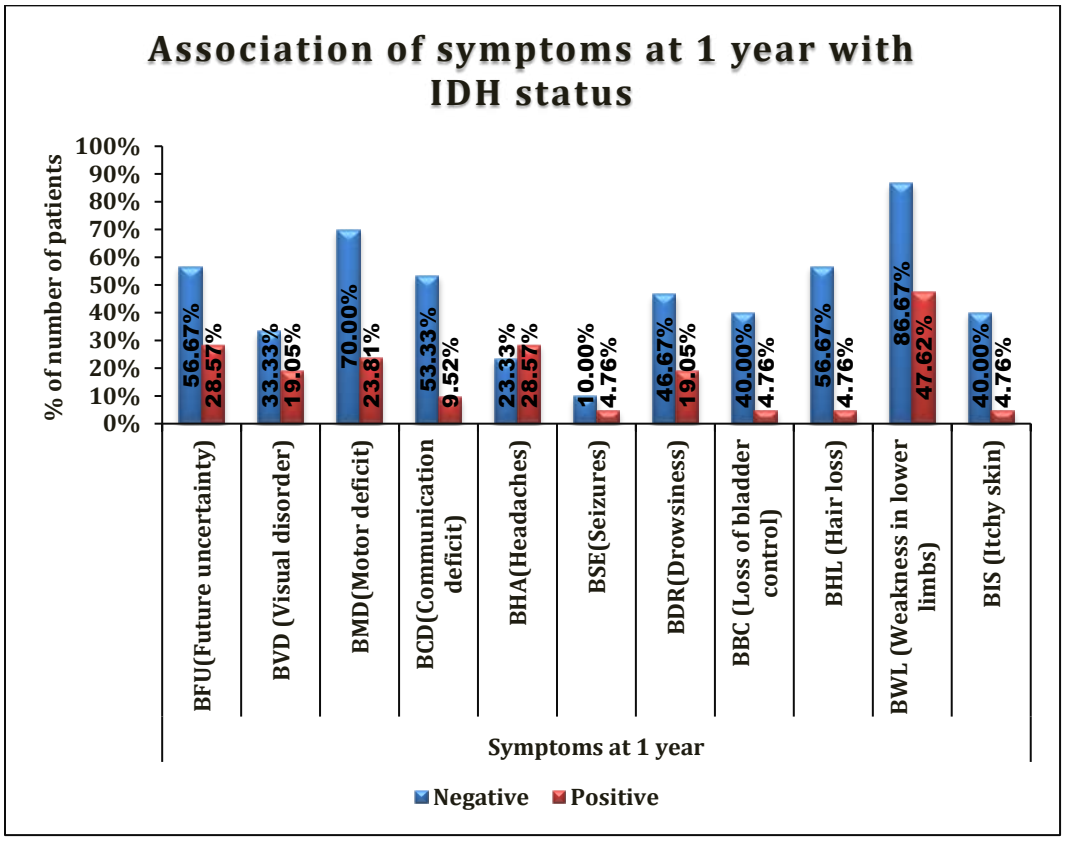

Figure 51:-Association of symptoms at 1 year with IDH status.

Compared to negative IDH status, positive IDH status had significantly lower proportion of patients with following symptoms at 1 year: future uncertainty (28.57% vs. 56.67%, p value = 0.047), motor deficit (23.81% vs. 70%, p value = 0.001), communication deficit (9.52% vs. 53.33%, p value = 0.002), loss of bladder control (4.76% vs. 40%, p value = 0.007), hair loss (4.76% vs. 56.67%, p value = 0.0001), weakness in lower limbs (47.62% vs. 86.67%, p value = 0.004) and itchy skin (4.76% vs. 40%, p value = 0.007).

There was no significant difference in proportions of visual disorder (positive: 19.05% vs. negative: 33.33%, p = 0.346), headaches (28.57% vs. 23.33%, p = 0.673), seizures (4.76% vs. 10%, p = 0.634) and drowsiness (19.05% vs. 46.67%, p = 0.073) between groups (Table 51, Figure 51).

Table 52:-Association of outcome with IDH status.

Outcome	Negative	Positive	Total	P value
Outcome				
Alive	17 (44.74%)	19 (86.36%)	36 (60%)	0.002*
Died	21 (55.26%)	3 (13.64%)	24 (40%)	
Overall survival(months)				
Mean ± SD	11.67 ± 5.23	11.33 ± 8.96	11.62 ± 5.54	0.759§
Median(25th-75th percentile)	14(7-15)	16(8.5-16.5)	14(6.75-16)	
Range	2-19	1-17	1-19	

§ **Mann Whitney test,** * **Fisher's exact test**

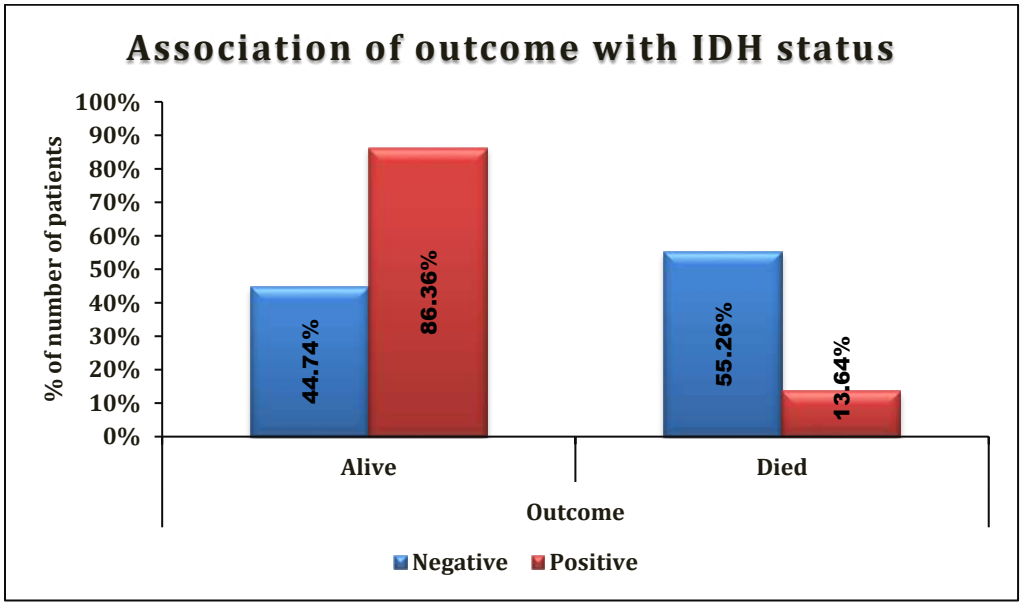

Figure 52.1:-Association of outcome with IDH status.

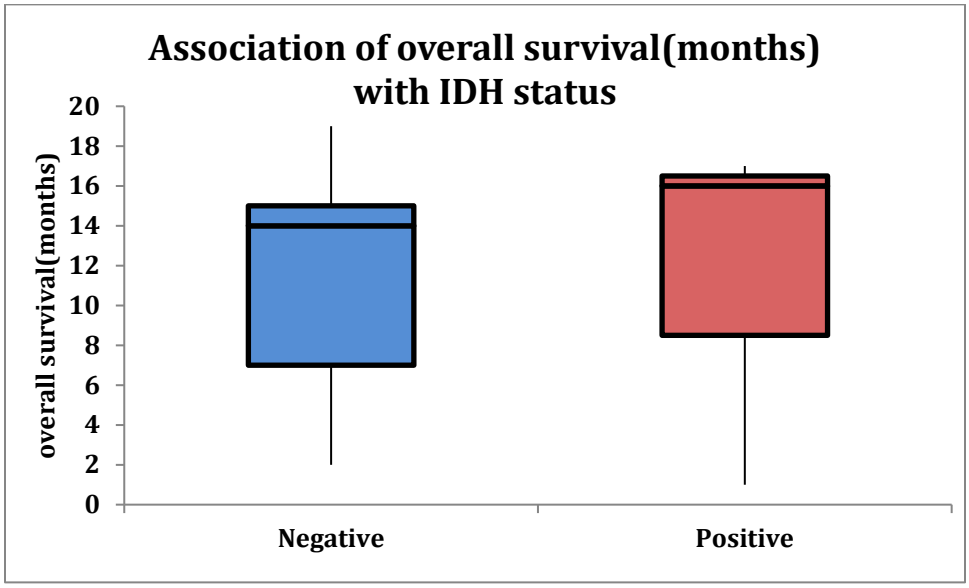

Figure 52.2:-Association of overall survival with IDH status.(non-parametric variable, Box-whisker plot)

Compared to negative IDH status, positive IDH status had significantly lower proportion of died patients (13.64% vs. 55.26%) and significantly higher proportion of patients who were alive (86.36% vs. 44.74%) (p value = 0.002). Median (25th-75th percentile) overall survival was 16 (8.5-16.5) months in positive group vs. 14 (7-15) months in negative group, with no significant association between them (p value = 0.759) (Table 52, Figure 52).

DISCUSSION

a. Demographic and General characteristics of Glioma patients

Hospital based brain tumor registries provide data on the magnitude and distribution of brain tumors in a given hospital. Singh,S. et al used glioma focused registry in their institute and studied demographic profile of glioma patients over a period of 12 years.[39] A total of 1450 patients were studied and the mean age of patients was found to be 39.3(±17.36 SD).Males comprised 66.6% of the patients.70.8% of the patients were between the age group of 18-60 (economically active age group).Glioblastoma was the most common tumor on histopathology (41.4%) followed by astrocytoma (22.8%).76% of patients above the age of 50 had WHO Grade 4 tumor on histopathology where as WHO Grade 1 and 2 were the most common tumor types in patients less than 18 years of age. Frontal lobe was the most common site involved (29% of patients).

Larjavaara S et al studied the incidence of gliomas by anatomic location in 331 patients.They found that frontal lobes were the most common location for gliomas found in 40% patients followed by temporal (29%), parietal (14%) and occipital (3%) lobes.[40]

A prospective study done at Tata Memorial Hospital,one of India's leading cancer centers included 656 patients, 254 of them were gliomas. 59.4% of these patients had high grade gliomas. Glioblastoma was the most common tumor.These findings correlate with other Indian data with respect to gliomas.

Jha et al reported the first series of Indian patients with glioma an IDH mutations were found in 68.8%,85.7% and 12.8% of all Grade II, III and glioblastomas respectively.40Another series also published similar number of glioblastoma patients with IDH mutations (12.5%).[41]

Mutations in p53 are the most common in glioma. Immunohistochemical studies detect high rates of p53 overexpression in high grade gliomas and higher immunopositivity in glioblastoma reflects the physiological accumulation of wild type p53 protein as a response to deregulated proliferation or DNA damage.

Ki67/MIB 1 immunostaining has been shown to correlate positively with tumor grade and prognosis.In a study conducted by Skjulsvik AJ et al, Ki67/MIB1 correlated significantly with

tumor grade for each glioma type although considerable overlap was observed between the malignancy groups.[42] Krishnan SS et al in their study found that there was a significant correlation between MIB1 index and high grade glioma and suggested that MIB index can be used as a prognostic tool.[38]

Positive reaction to GFAP has been observed in astrocytic tumors,ependymomas and pleomorphic xanthoastrocytomas. GFAP delta isoforms predict invasiveness of tumors and increased expression is highlighted in high grade gliomas compared to low grade tumors.[43] Unlike studies on IDH,the results are not consistent and other studies have studied data concluding to the extent that GFAP is not a reliable marker in predicting tumor behavior.Still others, have provided contrasting evidence concluding that GFAP, being a marker of differentiation is well expressed in differentiated slowly growing tumors and lesser in invasive tumors.[44]

The demographic profile and general characteristics of glioma patients in our study is comparable to the data as discussed above.

Mean age of glioma patients in our study was 39.45 ± 14.1 years. Out of the 60 patients stud ied, 44 (73.33%) were males and 16 (26.67%) were females. 24 patients(40.00%) cases had seizures making it the most common symptom on presentation, with headache and motor weakness each being present in 13 patients.(21.67%).37 (61.67%) cases had neurological deficit while 23 (38.33%) cases did not have neurological deficit on presentation.

Comparable to other studies, most common site of glioma in our study was the frontal lobe being involved in 19 (26.66%) patients. 88.33% (53 cases) had tumors which were located in the lateral brain.(hemispheric). 45 (75.00%) cases had high grade and 15 (25.00%) cases had low grade glioma. Glioblastoma (Grade IV) was the most common tumor type on histopathology seen in 28(46.67%) of the 45 cases.

On immunohistochemical studies,38 (63.33%) cases were IDH negative (IDH wildtype) and 22 (36.67%) cases were positive (IDH mutant).44 (73.33%) cases had retained nuclear expression of ATRX while 16 (26.67%) cases had loss of expression.37 (61.67%) cases were p53 negative and 23 (38.33%) cases were positive. MIB index of 0% to 5% was present in 16 (26.67%) cases. 37 (61.67%) cases were found to be negative for Olig 2 and 23 (38.33%) cases were positive.51 (85.00%) cases were negative for GFAP and 9 (15.00%) cases were positive.

b. Long term outcomes of high grade glioma

In a study of 1502 glioma patients conducted over a period of 18 years from 2000 to 2018, the average age of diagnosis of Grade I glioma was 21.9 years and that of Grade IV glioma was 46.3 years.The mean age of Grade II an Grade III gliomas was found to be 33.6 years and 38.9 years respectively. Hence, the study concluded that the grade of glioma patients increases with mean age. Three groups were stratified with pediatric age group from 0-14 years, young age group from 15-47 years, middle age group from 48-63 years and elderly age group equal to or more than 64 years.The proportion of patients with high grade glioma increased significantly with age.[45]

Clinician reported outcomes including KPS an ECOG have been extensively used across clinical trials for malignant gliomas. These scales are designed to quantify a given patient's functional capacity and activities of daily living from a clinician's perspective. KPS, along with being an outcome assessment tool, has also been regarded as a prognostic factor in overall survival of malignant glioma patients.

In a retrospective observational cohort study conducted on 91 patients with high grade glioma, functional status was observed using the KPS. It was seen that the survival rate of high grade glioma patients after one year of ICU admission was 27% and most patients presented with a favorable performance status with KPS > 60. This was a significant observation considering the median survival of high grade gliomas.[46]

Along with clinician reported outcomes to assess functional status, it is important to include patient reported outcomes (PRO) with respect to health related quality of life. Such PROs are assessed with the help of questionnaires like EORTC-QLQ-BN 20 specifically designed for brain tumors. This questionnaire assesses 11 endpoints: future uncertainty, visual deficit, communication difficulty, motor weakness, seizures, presence of headache, drowsiness, weakness of lower limbs, hair loss, loss of bladder control and itching of skin. Bosma I et al performed a large nationwide longitudinal study on health related quality of life of high and low grade glioma patients and used these endpoints as identifiers of brain tumor and treatment specific symptoms. They concluded that long term survivors of gliomas suffered significantly less from future uncertainty at 8,12 and 16 month follow ups compared o their baseline evaluation. They also had fewer headaches and less weakness of legs at 12 month follow up.[47]

Overall survival of patients with glioblastoma is bleak. The median survival in cancer registry databases ranges from 6-10 months. It is between 14.6-21.1 months in those treated with standard therapy in clinical trials.[48,49,50]

The results obtained in this study are comparable with other studies.

15 patients (25%) in this study are above the age of 50 years. All of them had high grade glioma. Mean ± SD of age in high grading group was 43.71 ± 12.38 years, which was significantly higher compared to low grading group (26.67 ± 11.19 years).

Compared to low grading group, high grading group in this study had significantly lower proportion of patients with ECOG score 0 at 6 months (7.5% vs. 86.67%) and significantly higher proportion with ECOG scores of 1 (55% vs. 6.67%), 2 (22.5% vs. 6.67%), 3 (5% vs. 0%) and 4 (10% vs. 0%). At 1 year, high grading group had significantly higher proportions with ECOG scores of 1 (50% vs. 13.33%), 3 (11.11% vs. 0%) and 4 (25% vs. 0%) and significantly lower proportions with scores of 0 (2.78% vs. 73.33%).

KPS at 6 months and KPS at 1 year were significantly associated with glioma grade. Mean ± SD of KPS at 6 months and 1 year was significantly lower in high grading group (72.75 ± 23.53 vs. 96.67 ± 9, 63.06 ± 30.97 vs. 92 ± 14.74) compared to low grading group

In this study, ECOG and KPS represented clinician reported long term outcomes of high grade glioma. The above results show that higher grade gliomas have a poor clinician reported long term outcome at 6 months and 1 year when compared to low grade gliomas.

The patient reported outcomes were assessed at 1 year follow up. Compared to low grading group, high grading group had significantly higher proportion of patients experiencing various symptoms at 1 year: future uncertainty (61.11% vs. 6.67%), motor deficit (66.67% vs. 13.33%), communication deficit (47.22% vs. 6.67%), headaches (36.11% vs. 0%), drowsiness (47.22% vs. 6.67%), loss of bladder control (36.11% vs. 0%), hair loss (50% vs. 0%) and weakness in lower limbs (91.67% vs. 20%). These results show that high grade gliomas had poor patient reported outcomes at 1 year.

There was no significant difference between groups for visual disorder (33.33% in high group vs. 13.33% in low group), seizures (11.11% vs. 0%) or itchy skin (30.56% vs. 13.33%)

Compared to low grading group, high grading group had significantly lower proportion of alive patients (46.67% vs. 100%) and significantly higher proportion of died patients (53.33% vs. 0%).Hence outcomes of high grade glioma were poor.

Mean ± SD of overall survival in high grading group was 11.62 ± 5.54 months with median (25th-75th percentile) of 14 (6.75-16) months. None of the patients with low grade glioma expired in this period of 2 years.

c. Correlation of High Grade Gliomas with Immunohistochemical markers

Immunohistochemistry was originally described by Coons et al. in 1941.They developed immunofluorescence technique to detect corresponding antigens in frozen sections. This technique exploits the specificity of antigen-antibody relations in light microscopy.[51]Since its discovery, IHC has become indispensable to surgical pathology. For using IHC, one should have knowledge regarding the ability of the specific tissue to express and antigen and the exact location of the antigen within the cell.

In a study of 115 glioma patients done in North India aimed at correlating the clinicopathological findings with immunohistochemical markers, it was found that 54 patients (46.95%) were IDH positive, 34 patients (29.56%) had loss of ATRX expression, 60 patients (52.17%) were p53 positive and 69 patients (60%) had Ki67 index of >5%.Only a small proportion of patients with GBM were IDH positive. (14 out of 45 cases, 31.11%) . p53 was positive in 77 patients (66.95%), most of which were Grade3 and Grade 4 tumors. Many recurrent tumors were also p53 positive.[52]

Mokhtari et al. investigated the expression of Olig 2 and GFAP in a series of 146 samples found out mutual exclusion at cell level of Olig 2 and GFAP expression.Pure oligodendrogliomas were Olig 2 positive an GFAP negative whereas astrocytomas and oligoastrocytomas were either Olig 2 positive, GFAP negative or Olig 2 negative, GFAP positive.[53]

The correlation of high grade gliomas with IHC in our study is as follows:

Compared to low grading group, high grading group had lower proportion of patients with positive IDH status (24.44% vs. 73.33%) and higher proportion with negative IDH status (75.56% vs. 26.67%). Compared to low grading group, high grading group had significantly lower proportion of patients showing loss of ATRX expression (20% vs. 46.67%) and significantly higher proportion with retained nuclear expression (80% vs. 53.33%). The high and low grade glioma group had comparable distribution of p53 status: negative status was 66.67% in high group vs. 46.67% in low group, while positive status was 33.33% vs.

53.33% respectively. All patients with MIB index of greater than 15% were high grade gliomas while 80% of patients with MIB from 0-5% were low grade gliomas suggesting a significant correlation between grade of glioma with MIB index.Compared to low grade glioma group, high grade group had significantly lower proportion of patients with positive olig2 status (28.89% vs. 66.67%) and significantly higher proportion with negative olig2 status (71.11% vs. 33.33%).High and low grade glioma groups had comparable distribution of GFAP: negative status was 84.44% in high group vs. 86.67% in low group, while positive status was 15.56% vs. 13.33% respectively.

d. Clinical evolution of IDH positive gliomas

Two molecular alterations have a high prevalence in low grade glioma: MGMT gene promoter methylation and IDH1/2 mutations. IDH 1 R132 is the most common IDH mutation in glioma. These mutations occur in 70-80% of low grade gliomas, 85% of secondary GBMs and in only 3-7% of primary GBMs.[54] The IDH gene product that normally converts isocitrate into alpha-ketoglutarate, when mutated, result in enzyme products that instead convert isocitrate into 2-hydroxyglutarate (2HG) which competitively inhibits downstream histone demethylases contributing to abnormal regulation of gene expression in these cancers.Mutations in IDH do not occur in pilocytic astrocytomas of WHO Grade I indicating that these tumors arise from a different mechanism.

A systematic review of literature on this subject was done by Khan I et al. In this review they evaluated the prognostic significance of IDH1 mutation based on published evidence. Multiple retrospective clinical analyses also correlate the presence of IDH1 mutation in GBM with better prognostic outcomes when compared to wild-type IDH1. The systematic review reported similar results. Based on the current literature, IDH1 mutation is an independent factor for longer overall survival (OS) and progression free survival (PFS) in GBM patients when compared to wild-type IDH1[20]

In the landmark study done by Yan H et al, the following observations were made: Glioma patients harbouring mutations in IDH1/2 were younger than patients with wildtype IDH genes. (34 years vs. 56 years for anaplastic astrocytomas and 32 years vs. 59 years for glioblastomas)Patients with glioblastoma harbouring mutations in IDH1/2 had a median overall survival of 31 months as opposed to 15 months for IDH negative tumors.80% of the tumors with

mutated IDH1/2 genes also had a mutation of p53 while only 18% of IDH wildtype tumors had p53 mutations.Loss of 1p and 19q was observed in 85% of oligodendrocytic tumors with mutated IDH1/2 but in none of the wildtype IDH tumors.[55]

With respect to patient reported outcomes S. Lee et al. conducted a study on 61 patients with high grade glioma who underwent surgery. They recorded their preoperative health related quality of life score with EORTC-QLQ-BN 20 (the questionnaire we used in this study)and cognitive function and compared it with their postoperative scores. They concluded that post operative HRQOL score and cognitive functions were better in IDH mutant as compared to IDH wild type tumors.[56]

Contrary to the results published by Yan H et al, Amelot A et al. conducted a retrospective study of 207 GBM patients done between 2005 and 2010. Mutations of IDH1/2 were analyzed and mutation rates in long term survivors and non long term survivor groups were compared by Chi square test. They established that the difference in the rate of IDH mutation between non long term survivors and long term survivors was not statistically significant (1.16% vs. 5.9%, p=0.144) and concluded that long term survival is if at all only weakly correlated to IDH mutation.[57]

Description of the clinical evolution of IDH positive tumors is done in this study and is comparable with other studies as mentioned above.

Out of the 60 patients included in our study, 22 patients (36.66%) were IDH positive or IDH mutant. 38 patients (63.33%) were IDH negative. The maximum number of IDH positive tumors that is 8 out of 22 (36.36%) were clustered in the age range of 31 to 40 years followed by 21 to 30 years of age which comprised of 7 patients (31.81%). Mean ± SD age was 34.95 ± 10.52 years in positive group vs. 42.05 ± 15.37 years in negative group. Of the 22 patients, 17 were males (77.27%) and 5 were female (22.72%).

Seizure was the most common presenting symptom in the IDH positive group. It was present as the initial symptom in 10 out of 22 patients.(45.45%) followed by motor weakness in 6 patients (27.27%). IDH positive tumors had an equal number of patients presenting with and without neurological deficit. (11 patients in both groups, 50%)

Frontal lobe was the most common afected lobe in IDH positive group involved in 10 out of 22 patients (45.45%). Most of the tumors in this group (20 out of 22, 90.91%) were hemispheric in location and 2 were located in the midline.

Compared to negative IDH group, positive IDH group had significantly lower proportion of patients with WHO grade I (4.55% vs. 10.53%) and grade IV (9.09% vs. 68.42%) tumors. Conversely, proportion of patients with WHO grade II (45.45% vs. 10.53%) and grade III (40.91% vs. 10.53%) was significantly higher in positive IDH group compared to the negative group. The lower proportion of IDH positive patients with grade I tumors is due to its absence in pilocytic astrocytoma as discussed above. As IDH mutations occur only in 3-7% of patients with primary GBM, it is present in low proportions in Grade IV tumors in this study.

The positive IDH group retained nuclear expression of ATRX in 59.09% (13 out of 22) patients. 50% of the positive IDH tumor patients were negative for p53 and 50% were p53 positive. In the IDH mutant group, 16 patients (72.72%) had MIB index ranging from 0 to 10%. 45.45% of the patients (10 out of 22) in IDH mutant group were positive for Olig 2. The IDH mutant group had no patients who tested GFAP positive.

The clinical evolution of these tumors is being discussed with respect to its outcomes.

The clinician reported outcomes of these tumors have been studied using KPS and ECOG scores. At 6 months follow up, the IDH positive tumor group had significantly lower proportion of patients with ECOG 1,2,3 and 4 (33.33%,4.76%,0% and 0% respectively) and a significantly higher proportion of patients with ECOG 0 (61.90%). At 1 year follow up, IDH positive group had significantly lower proportion of patients with ECOG 3 and 4 (0% and 0% respectively) and significantly higher proportion of patients with ECOG 0,1and 2 (42.86%,42.86% and 14.29% respectively). Mean ± SD of KPS at 6 months and KPS at 1 year in positive IDH status was 92.38 ± 9.95 and 86.67 ± 14.26 respectively, which was significantly higher compared to negative IDH status (71.18 ± 25.32)

The patient reported outcomes of IDH positive tumors were studied based on symptoms mentioned in the EORTC-QLQ-BN20 questionnaire which studies health related quality of life. Compared to the IDH negative group, the positive IDH group had significantly lower proportion of patients with following symptoms at 1 year: future uncertainty (28.57% vs. 56.67%), motor deficit (23.81% vs. 70%), communication deficit (9.52% vs. 53.33%), loss of bladder control (4.76% vs. 40%), hair loss (4.76% vs. 56.67%), weakness in lower limbs (47.62% vs. 86.67%) and itchy skin (4.76% vs. 40%).There was no significant difference in proportions of visual disorder (positive: 19.05% vs. negative: 33.33%), headaches (28.57% vs. 23.33%), seizures (4.76% vs. 10%) and drowsiness (19.05% vs. 46.67%) between groups

Compared to negative IDH status, positive IDH status had significantly lower proportion of patients who died (13.64% vs. 55.26%) and significantly higher proportion of patients who were alive (86.36% vs. 44.74%). Median (25th-75th percentile) overall survival was 16 (8.5-16.5) months in positive group vs. 14 (7-15) months in negative group, with no significant association between them.

CONCLUSION

After considering findings in other studies and comparing various parameters in this study regarding the long term outcomes of high grade glioma, its correlation with immunohistochemical markers and the clinical evolution of IDH positive tumors, the following conclusions were drawn:

- Glioma, is not a disease of the elderly as considered previously. The mean age is 39 years in our study and it corresponds well with other national and international studies. They are mostly hemispheric in location and the frontal lobes are most commonly involved. Seizures might be the initial symptom in many patients and therefore it should be thoroughly investigated. Neurological deficits are variably present. Most common tumor type is glioblastoma. Immunohistochemical analysis of molecular markers like IDH, ATRX, p53, MIB 1index, Olig 2 and GFAP is extremely important for further classification and prognostication.
- High grade gliomas are more common with increasing age. The long term outcomes which were studied with respect to clinician and patient reported outcomes were significantly poor when compared to low grade gliomas. Patients with high grade gliomas had a higher ECOG grade and a lower KPS at 6 months and 1 year follow up. They had a greater proportion of patients having one or more symptoms of future uncertainty, motor deficit, communication difficulty, weakness of lower limbs, headache, loss of bladder control, hairloss and drowsiness. There were significantly lower number of alive patients with high grade glioma at the end of the study and the mean survival amongst those who expired was 11.62 ± 5.54 months
- High grade gliomas had a significant association with some but not all molecular markers. They had a significantly larger proportion of patients with IDH wildtype tumors. They also had a significantly larger proportion of patients showing retained nuclear expression of ATRX. High grade glioma patients had a significantly lower proportion of samples with MIB index from 0 to 5% whereas all samples with MIB index greater than 10% were high grade gliomas. This is important clinically reconfirming Ki67/MIB1 inex as a marker of proliferation.The high grade group had a significant proportion of samples

with negative Olig 2 status. There was no significant association of high grade gliomas with p53 and GFAP in this study.

- High grade gliomas were studied for their histopathological characteristics. High grade gliomas have a significantly large proportion of samples exhibiting high cellularity, high mitotic activity and high nuclear atypia. They also have a significantly larger proportion of samples that show microvascular proliferation and necrosis.
- In this study, IDH positive tumors had a comparable distribution with IDH negative tumors with respect to age, gender, symptomatology, presence of neurological deficit and lobe/ region of brain involved. IDH positive tumors had a significantly greater proportion of patients with grade II and grade III tumors. The immunohistochemical profile of IDH positive and IDH negative tumors with respect to other markers were comparable except that the IDH mutant group had no samples which were GFAP positive. At 6 months and 1 year follow up, IDH mutant group had significantly greater proportion of patients with lower ECOG grade and higher KPS. This correlated with patient reported outcomes as they had significantly decreased proportion of patients having symptoms of future uncertainty, motor deficit, communication difficulty, weakness of lower limbs, loss of bladder control, hairloss and itching of skin at 1 year follow up. Although there was no significant association in overall survival between IDH mutant and wildtype tumors amongst those who died, there was a significant higher proportion of IDH positive patients who were alive at the end of the study.

LIMITATIONS

Although all procedures and methods involved in the study were as per standard scientific recommendations, certain inevitable limitations remain:

The study was done in a single institution. It is a combined prospective and retrospective observational cohort study and not free from selection and confounding bias.

The sample size of 60 glioma patients would be considered small considering the large pool of patients in this category. International studies have a larger sample size.

In molecular studies, 1p19q codeletion is an important parameter to identify oligodendroglioma which was not routinely performed in our cohort and not assessed in our study.

Although all surgeons were of the same experience and capability, differences in surgical skills could affect postoperative long term outcome

In the academic time frame available, the study was performed in a limited time span and hence longer follow up period could not be included. This would be important for patients with longer life spans like low grade glioma and IDH positive tumors.

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ANNEXURES

1.Participant Information Sheet

1 STUDY TITLE:STUDY OF THE LONG TERM OUTCOMES FO HGIH GRADE GLIOMAS, THEIR CORRELATION WITH IMMUNOHISTOCHEMICAL MARKERS AND THE CLINICAL EVOLUTION OF ISOCITRATE DEHYDROGENASE POSITIVE TUMORS

2 STUDY INVESTIGATORS:

Student:Dr Abhishek Latish Shetty,Senior Resident,Dept of Neurosurgery

Guide : Dr Adesh Shrivastava, Additional Professor,Dept of Neurosurgery

Co-Guides Dr Sumit Raj, Additional Professor,Dept of Neurosurgery

Dr Amit Aggarwal, Professor and Head,Dept of Neurosurgery .

3. Introduction

We are conducting a research to study the long term outcomes of high grade gliomas, their correlation with immunohistochemical markers and the clinical evolution of isocitrate dehydrogenase positive tumors in AIMS Bhopal. We would like to examine you clinically, radiologically and send your pathological investigations. If you agree to take part voluntarily, we will ask you to sign a consent form.

4. Purpose of the study:

The aim of our study is to study the long term outcomes of high grade gliomas and analyze how they correlate with immunohistochemical markers and study the clinical evolution of isocitrate dehydrogenase positive tumors This will help us formulate further management of patients with gliomas.

5. Taking part - what it involves:

a. Do I have to take part?

Participation in this research is entirely voluntary. A decision to not take part or to withdraw at any time, will not affect your rights or medical care in any way

b. What is expected of me if I take part?

If you participate, we will collect all details of your operative history and examine your pathological samples and send immunohistochemical assay for further analysis.

c. How long will my part in the study last?

Your participation in the study would last for 18 months

d. Do I have to come for extra visits or undergo extra investigations for the study?

Yes,at 6 months and 1 year you will be followed up and advised basic investigations like complete blood count, liver and renal function test.

e. What are the possible benefits in taking part?

Taking part will help gain knowledge about management of patients with glioma and understand how isocitrate dehydrogenase positive tumors evolve clinically which may result in improvement of management and outcomes for you / patients like yourself.

f. What are the possible disadvantages and risks of taking part?

There are no major foreseeable disadvantages or risks because of the study. There may be risk of loss of privacy and confidentiality of information collected even though all possible measures will be taken to ensure safe data storage and access.

g. What happens to the information collected from me?

All information collected will be kept strictly confidential and not shared with anyone. Results from the study will be reported as group data and will not identify you in any way.

h.What if I change my mind regarding participation in the study?

You are entitled to change your mind and withdraw at any time during the study without any disadvantage or penalty..

i.Whom do I contact for more information or if I have further questions or concerns?

If you want any information or have questions or concerns, you can contact:

Dr. Abhishek Latish Shetty	Dr. Shashank Purwar
Senior Resident, Neurosurgery	Member Secretary
AIIMS Bhopal	Institute Ethics Committee -Student Research
9653654701	7773010099,

प्रतिभागी सूचना पत्रक

1 अध्ययन का शीर्षक: उच्च ग्रेड ग्लिओमास के दीर्घकालिक परिणामों के लिए अध्ययन, इम्यूनोहिस्टोकेमिकल मार्करों के साथ उनका सहसंबंध और आइसोसिट्रेट डिहाइड्रोजनेज पॉजिटिव ट्यूमर का नैदानिक विकास

2 अध्ययन अन्वेषक:

छात्र: डॉ. अभिषेक लतीश शेट्टी, सीनियर रेजिडेंट, न्यूरोसर्जरी विभाग

मार्गदर्शक: डॉ. आदेश श्रीवास्तव, अतिरिक्त प्रोफेसर, न्यूरोसर्जरी विभाग

सह-मार्गदर्शक डॉ. सुमित राज, अतिरिक्त प्रोफेसर, न्यूरोसर्जरी विभाग

डॉ अमित अग्रवाल, प्रोफेसर और प्रमुख, न्यूरोसर्जरी विभाग।

3. परिचय

हम एआईएमएस भोपाल में उच्च ग्रेड ग्लियोमास के दीर्घकालिक परिणामों, इम्यूनोहिस्टोकेमिकल मार्करों के साथ उनके सहसंबंध और आइसोसिट्रेट डिहाइड्रोजनेज पॉजिटिव ट्यूमर के नैदानिक विकास का अध्ययन करने के लिए एक शोध कर रहे हैं। हम आपकी चिकित्सकीय, रेडियोलॉजिकल जांच करना चाहते हैं और आपकी पैथोलॉजिकल जांच भेजना चाहते हैं। यदि आप स्वेच्छा से भाग लेने के लिए सहमत हैं, तो हम आपसे एक सहमति प्रपत्र पर हस्ताक्षर करने के लिए कहेंगे।

4. अध्ययन का उद्देश्य:

हमारे अध्ययन का उद्देश्य उच्च ग्रेड ग्लियोमास के दीर्घकालिक परिणामों का अध्ययन करना और विश्लेषण करना है कि वे इम्यूनोहिस्टोकेमिकल मार्करों के साथ कैसे संबंधित हैं और आइसोसाइट्रेट डिहाइड्रोजनेज पॉजिटिव ट्यूमर के नैदानिक विकास का अध्ययन करते हैं। इससे हमें ग्लियोमास वाले रोगियों के आगे के प्रबंधन को तैयार करने में मदद मिलेगी।

5. भाग लेना - इसमें क्या शामिल है:

a. क्या मुझे भाग लेना होगा?

इस शोध में भागीदारी पूर्णतः स्वैच्छिक है। भाग न लेने या किसी भी समय वापस लेने का निर्णय किसी भी तरह से आपके अधिकारों या चिकित्सा देखभाल को प्रभावित नहीं करेगा

b. यदि मैं भाग लेता हूँ तो मुझसे क्या अपेक्षा की जाती है? यदि आप भाग लेते हैं, तो हम आपके ऑपरेटिव इतिहास के सभी विवरण एकत्र करेंगे और आपके पैथोलॉजिकल नमूनों की जांच करेंगे और आगे के विश्लेषण के लिए इम्यूनोहिस्टोकेमिकल परख भेजेंगे।

c. अध्ययन में मेरी भूमिका कितने समय तक रहेगी?

अध्ययन में आपकी भागीदारी 18 महीने तक रहेगी

d. क्या मुझे अतिरिक्त दौरे के लिए आना होगा या अध्ययन के लिए अतिरिक्त जांच से गुजरना होगा?

हां, 6 महीने और 1 साल की उम्र में आपकी निगरानी की जाएगी और संपूर्ण रक्त गणना, लीवर और रीनल फंक्शन टेस्ट जैसी बुनियादी जांच की सलाह दी जाएगी।

e. भाग लेने में संभावित लाभ क्या हैं?

भाग लेने से ग्लियोमा वाले रोगियों के प्रबंधन के बारे में ज्ञान प्राप्त करने में मदद मिलेगी और यह समझ आएगा कि आइसोसिट्रेट डिहाइड्रोजनेज पॉजिटिव ट्यूमर चिकित्सकीय रूप से कैसे विकसित होते हैं जिसके परिणामस्वरूप आपके/आप जैसे रोगियों के लिए प्रबंधन और परिणामों में सुधार हो सकता है।

f. भाग लेने के संभावित नुकसान और जोखिम क्या हैं?

अध्ययन के कारण कोई बड़े पूर्वानुमानित नुकसान या जोखिम नहीं हैं। एकत्र की गई जानकारी की गोपनीयता और गोपनीयता के नुकसान का जोखिम हो सकता है, भले ही सुरक्षित डेटा भंडारण और पहुंच सुनिश्चित करने के लिए सभी संभव उपाय किए जाएंगे।

g. मुझसे एकत्रित की गई जानकारी का क्या होता है?

एकत्र की गई सभी जानकारी पूरी तरह से गोपनीय रखी जाएगी और किसी के साथ साझा नहीं की जाएगी। अध्ययन के परिणाम समूह डेटा के रूप में रिपोर्ट किए जाएंगे और किसी भी तरह से आपकी पहचान नहीं की जाएगी।

h. यदि मैं अध्ययन में भाग लेने के संबंध में अपना मन बदल दूं तो क्या होगा?

आप अध्ययन के दौरान किसी भी समय अपना मन बदलने और बिना किसी नुकसान या दंड के पीछे हटने के हकदार हैं।

i.अधिक जानकारी के लिए या यदि मेरे कोई और प्रश्न या चिंताएँ हों तो मैं किससे संपर्क करूँ?

यदि आप कोई जानकारी चाहते हैं या कोई प्रश्न या चिंता है, तो आप संपर्क कर सकते हैं:

डॉ. अभिषेक लतीश शेट्टी
सीनियर रेजिडेंट, न्यूरोसर्जरी
एम्स भोपाल
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डॉ. शशांक पुरवार
सदस्य सचिव
इंस्टीट्यूट एथिक्स कमेटी-स्टूडेंट रिसर्च
7773010099

प्रतिभागी सूचना सहमति प्रपत्र [PARTICIPANT INFORMED CONSENT FORM (PICF)]

अध्ययन के लिए प्रतिभागी का पहचान नंबर / Participant Identification Number for Study: ……

अनुसंधान का शीर्षक / Title of Project : "उच्च ग्रेड ग्लिओमास के दीर्घकालिक परिणामों के लिए अध्ययन, इम्यूनोहिस्टोकेमिकल मार्करों के साथ उनका सहसंबंध और आइसोसिट्रेट डिहाइड्रोजनेज पॉजिटिव ट्यूमर का नैदानिक विकास STUDY OF THE LONG TERM OUTCOMES FO HGIH GRADE GLIOMAS, THEIR CORRELATION WITH IMMUNOHISTOCHEMICAL MARKERS AND THE CLINICAL EVOLUTION OF ISOCITRATE DEHYDROGENASE POSITIVE TUMORS

छात्र शोधकर्ता का नाम / Name of Student Investigator: डॉ. अभिषेक लतीश शेट्टी Dr Abhishek Latish Shetty Phone No. 9653654701

शोध मार्गदर्शक का नाम / Name of Thesis Guide: डॉ. आदेश श्रीवास्तव /Dr Adesh Shrivastava

मैंने संस्करण संख्या II दिनांक 20-08-2022 के सूचना पत्रक में दिए गए सभी तथ्यों को सावधानीपूर्वक पढ़ लिया है/ मुझे अपनी भाषा में स्पष्ट रूप से विस्तारपूर्वक समझा दिया गया है, और मैंने तथ्यों को पूर्णतः समझ लिया है। मैं पुष्टि करता/ करती हूँ, कि मुझे सवाल पूछने के अवसर प्रदान किए गए। The contents of the information sheet version II dated 20th August 2022 that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

मुझे इस अध्ययन की प्रकृति एवं उद्देश्य और इसके संभावित जोखिमों / लाभों तथा अध्ययन की अनुमानित अवधि एवं अन्य प्रासंगिक जानकारी के बारे में विस्तारपूर्वक समझा दिया गया है। मुझे पता है कि इस अध्ययन में मेरी भागीदारी स्वैच्छिक है तथा मैं इस अध्ययन से किसी भी समय बिना कोई कारण बताए, अपना नाम वापस लेने के लिए स्वतंत्र हूं और नाम वापस लेने पर मेरी चिकित्सा देखभाल या कानूनी अधिकारों पर कोई प्रभाव नहीं पड़ेगा। The nature and purpose of the study and its potential risks/benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation

is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

मैं समझता/समझती हूं कि इस अनुसंधान में मेरी भागीदारी से मेरे बारे में एकत्र की गई जानकारी और मेरे चिकित्सीय दस्तावेजों के किसी भी भाग को एम्स के जिम्मेदार व्यक्तियों द्वारा ही देखा जाएगा। मैं इन व्यक्तियों को मेरे रिकॉर्ड प्राप्त करने की अनुमति प्रदान करता/ करती हूँ। I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS. I give permission for these individuals to have access to my records.

यदि प्रतिभागी बच्चा है, तो उसकी मौखिक या लिखित सहमति प्राप्त की गई है। If participant is child, his / her verbal or written assent has been obtained.

मैं उक्त अध्ययन में भाग लेने के लिए सहमत हूं। I agree to take part in the above study.

_____

(प्रतिभागी के हस्ताक्षर / बांए अंगूठे का निशान) (Signature / Left Thumb Impression)

दिनांक/Date……स्थान/Place …….....

प्रतिभागी का नाम/Name of the participant …….....

पिता/पति/पत्नी का नाम /Son/Daughter/Spouse of…….

डाक का पूरा पता /Complete Postal Address ……....

अगर अशिक्षित हो / If illiterate,

सूचना पत्र को प्रतिभागी को पढ़ा और समझाया गया है, और प्रश्न पूछने का अवसर दिया गया है। मैं पुष्टि करता हूं कि व्यक्ति ने स्वतंत्र रूप से सहमति दी है।

The information sheet has been read and explained to the participant, and given the opportunity to ask questions. I confirm that the individual has given consent freely.

कानूनी रूप से स्वीकार्य प्रतिनिधि अथवा निष्पक्ष गवाह के हस्ताक्षर/Signature of Legally Acceptable Representative or impartial witness: _____

दिनांक / Date:

एलएआर अथवा निष्पक्ष गवाह का नाम / Name of LAR or impartial witness:

पता/Address:

प्रमाणित किया जाता है कि उक्त सहमति मेरी उपस्थिति में प्राप्त की गई ।

This is to certify that the above consent has been obtained in my presence.

_____

छात्र शोधकर्ता के हस्ताक्षर दिनांक……..स्थान……

Signature of the Student Investigator Date ……Place ……

कृपया ध्यान देः सहमति प्रपत्र तीन प्रतियों में (1) रोगी के लिए, (2) शोधकर्ता, (3) संस्थान के लिए तैयार करें ।Please note: Three copies should be made, for (1) Patient, (2) Researcher, (3) Institution

4.Case Record Form

1. IDENTIFYING INFORMATION

1.1. Name of Patient

1.2. Father's name

1.3. Age/Sex:

1.4. Registration Number:

1.5. Date of Registration:

1.6. Place of Residence

1.7. Occupation

1.8. Family income

1.9. Handedness

1.10Caregiver's name/relation with patient

2. DETAILS OF SYMPTOMS

2.1. Age of onset of symptoms

2.2 Age at diagnosis

2.3. Frequency of associated symptoms

2.4 H/o exposure to risk factors (radiation etc)

2.5 H/o previous surgeries/treatment taken

3. DETAILS OF EXAMINATION

3.1General survey

Head to toe examination

Vitals (pulse/BP/Respiratory rate, temperature)

Systemic examination

Higher mental functions

3.2. Cranial nerve functions

3.3 Motor functions

Tone

Power

Coordination

Involuntary movements

3.4 Sensory functions

Pain

Touch

Temperature

Two point discrimination

Stereognosis

3.5: Superficial reflexes

Abdominal

Cremastric

Plantar

3.6. Deep tendon jerks

Biceps jerk

Triceps jerk

Supinator jerk

Hoffman reflex

Knee jerk

Ankle jerk

3.6. Cerebellar signs

4. DETAILS OF SURGERY

Date of surgical procedure

Approach used

Intraoperative findings

Squash report

Biopsy report

Immunohistochemical assay

Post operative complications .

5 ASSESSMENT OF LONG TERM OUTCOME

Clinician reported outcomes:

Eastern Cooperative Oncology group performance status scale

Karnofsky performance score

Patient reported outcomes:

EORTC -QLQ-BN 20 questionnaire

Future uncertainty

Motor weakness

Communication difficulty

Visual deficit

Headache

Seizure

Drowsiness

Weakness of lower limbs

Loss of bladder control

Hairloss

Itching of skin

6. IMMUNOHISTOCHEMICAL MARKERS

IDH

ATRX

P53

MIB1 index

Olig 2

GFAP

MASTERCHART

#NAME?	sex	Age	Symptoms	Neurologi	Lobe	Region	WHO Grac	Grading	IDH status	ATRX stati	P53 status	MIB index	Olig 2	GFAP	Tumor typ	Cellularity	Mitotic ac	Nuclear at	Microvascular prolifera	Necrosis	Cause of death
1	M	36	seizures	present	lt tempor	Lateral bra	4	High	negative	retained r	negative	10-12%	positive	positive	Glioblasto	High	high	Moderate	present	present	Tumor progression
2	F	58	seizures	present	rt parieto	Lateral bra	4	High	negative	loss of ex	negative	10-12%	negative	negative	Glioblasto	High	high	Moderate	present	present	tumor progression
3	M	42	headache	absent	rt tempor	Lateral bra	4	High	negative	loss of ex	negative	15%	negative	positive	Glioblasto	moderate	high	Moderate	present	absent	tumor progression
4	M	30	headache	absent	left fronta	Lateral bra	3	High	positive	retained r	negative	15%	positive	negative	Anaplastic	High	high	Moderate	absent	absent	NA
5	M	54	motor weakness	present	lt parieto	Lateral bra	4	High	negative	retained r	negative	12%	negative	negative	Glioblasto	High	high	moderate	present	present	Tumor progression
6	M	38	motor weakness	present	rt frontal	Lateral bra	2	Low	positive	retained r	negative	3%	negative	negative	Oligodenr	High	low	Moderate	absent	absent	NA
7	M	47	seizures	absent	rt tempor	Lateral bra	3	High	positive	retained r	positive	10-12%	negative	negative	Oligoastro	High	high	high	present	present	NA
8	F	48	headache	absent	lt frontal	Lateral bra	3	High	positive	retained r	positive	10%	negative	negative	Anaplastic	High	high	high	present	present	Tumor progression
9	M	66	aphasia and dementia	present	lt parietal	Lateral bra	4	High	negative	loss of ex	negative	10%	negative	negative	Glioblasto	High	high	high	present	present	Tumor progression
10	F	40	headache	absent	rt parieto	Lateral bra	4	High	negative	retained r	negative	12-15%	positive	negative	Glioblasto	High	high	high	present	present	Tumor progression
11	M	23	motor weakness	present	lt frontal	Lateral bra	2	Low	positive	loss of ex	positive	2-3%	negative	negative	Astrocyto	moderate	low	Moderate	absent	absent	NA
12	M	21	visual disturbance	present	cerebral p	Midline	4	High	negative	loss of ex	positive	8-10%	positive	positive	Diffuse m	High	high	high	present	present	Tumor progression
13	M	50	headache	absent	rt parietal	Lateral bra	4	High	negative	retained r	positive	15-18%	negative	negative	Glioblasto	High	high	high	present	present	Tumor progression
14	M	23	motor weakness	present	rt frontote	Lateral bra	2	Low	positive	loss of ex	positive	5%	positive	negative	Astrocyto	moderate	low	Moderate	absent	absent	NA
15	M	50	visual disturbance	present	lt occipita	Lateral bra	4	High	negative	retained r	positive	15%	negative	negative	Glioblasto	High	high	Moderate	present	present	tumor ptogression
16	M	61	seizures	present	lt tempor	Lateral bra	4	High	negative	retained r	positive	15-18%	negative	negative	Glioblasto	moderate	high	Moderate	present	present	Tumor progression
17	F	42	seizures	absent	lt frontal	Lateral bra	3	High	negative	retained r	negative	8-10%	negative	negative	Astrocyto	moderate	high	Moderate	absent	absent	NA
18	M	68	motor weakness	present	rt frontal	Lateral bra	4	High	negative	retained r	negative	15%	negative	negative	Glioblasto	High	high	Moderate	present	present	Tumor progression
19	M	33	seizures	absent	lt insular	Lateral bra	2	Low	positive	loss of ex	positive	6-7%	positive	negative	Astrocyto	moderate	low	Moderate	absent	absent	NA
#NAME?	sex	Age	Symptoms	Neurologi	Lobe	Region	WHO Grac	Grading	IDH status	ATRX stati	P53 status	MIB index	Olig 3	GFAP	Tumor typ	Cellularity	Mitotic ac	Nuclear at	Microvascular prolifera	Necrosis	Cause of death

Surgical resection	Radiotherapy	Chemotherapy	Overall sur	KPS at 6 months	ECOG at 6	KPS at 1yr	ECOG at 1	BFU(futur	BVD (visu	BMD(mot	BCD(comr	BHA(head	BSE(seizu	BDR(drow	BBC (loss	BHL (hairl	BWL (wea	BIS (itchy s
gross total excision	yes	yes	16months	80	1	40	3	yes	no	yes	yes	no	no	yes	yes	yes	yes	yes
gross total excision	yes	yes	14months	50	2	20	4	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	yes
gross total excision	yes	yes	18months	60	2	40	3	yes	no	yes	yes	yes	no	no	no	yes	yes	yes
gross total excision	yes	yes	NA	80	1	80	1	no	no	yes	yes	yes	no	no	no	no	yes	no
gross total excision	yes	yes	19 months	40	3	20	4	yes	no	yes	yes	no	no	yes	yes	yes	yes	yes
gross total excision	yes	yes	NA	100	0	80	1	no	no	no	no	no	no	no	no	no	no	no
gross total excision	yes	yes	NA	100	0	80	1	no	no	yes	no	yes	no	no	no	no	yes	no
gross total excision	yes	yes	17months	80	1	60	2	yes	yes	no	no	yes	yes	yes	yes	yes	yes	no
gross total excision	yes	yes	14months	80	1	20	4	yes	no	yes	yes	no	no	yes	yes	yes	yes	no
gross total excision	yes	yes	18months	60	2	40	3	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
gross total excision	yes	no	NA	100	0	100	0	no	no	no	no	no	no	no	no	no	no	no
gross total excision	yes	yes	14months	50	2	10	4	yes	yes	yes	yes	no	no	yes	yes	yes	yes	yes
gross total excision	yes	yes	14months	60	2	20	4	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	yes
gross total excision	yes	yes	NA	100	0	100	0	yes	no	no	no	no	no	no	no	no	no	no
gross total excision	yes	yes	16months	80	1	40	3	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	no
subtotal resection	no	no	3.5months	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
gross total excision	yes	no	NA	60	2	80	1	no	no	yes	yes	no	no	no	no	no	yes	no
gross total excision	yes	yes	15months	50	2	40	4	yes	yes	yes	yes	no	no	yes	yes	yes	yes	yes
gross total excision	yes	no	NA	100	0	100	0	no	no	no	no	no	no	no	no	no	no	no

21	M	42	seizures	present	rt tempor	Lateral bra	4	High	negative	retained r	negative	18-20%	negative	negative	Glioblastc	High	high	high	present	present	Tumor progression
22	M	52	seizures	present	rt tempor	Lateral bra	4	High	negative	retained r	positive	18%	negative	negative	Glioblastc	High	high	Moderate	present	present	Tumor progression
23	F	56	motor weakness	present	rt frontop	Lateral bra	3	High	positive	retained r	negative	8-10%	negative	negative	Oligodenc	High	high	Moderate	absent	absent	tumor progression
24	F	33	motor weakness	present	lt frontal	Lateral bra	3	High	negative	retained r	negative	8%	positive	negative	Oligoastrc	High	low	mild	absent	absent	NA
25	M	36	seizures	absent	rt parieto-	Lateral bra	4	High	positive	loss of ex	negative	12%	positive	negative	Astrocyto	High	high	high	present	present	tumor progrssion,c
26	F	19	visual disturbance	present	suprasella	Midline	1	Low	negative	retained r	negative	2-3%	positive	negative	Pilocytic a	moderate	low	Moderate	absent	absent	NA
27	F	70	seizures	absent	lt parietal	Lateral bra	4	High	negative	loss of ex	negative	10-12%	negative	negative	Glioblastc	High	high	high	present	present	tumor progression
28	M	10	visual disturbance	present	fourth ver	Midline	1	Low	negative	retained r	negative	1-2%	positive	positive	Pilocytic a	low	low	mild	present	absent	NA
29	M	42	seizures	absent	lt frontal	Lateral bra	2	Low	positive	retained r	negative	8-10%	negative	negative	Oligodenc	moderate	high	Moderate	absent	absent	NA
30	M	35	seizures	absent	lt frontote	Lateral bra	3	High	positive	retained r	negative	12%	negative	negative	Oligodenc	High	high	Moderate	absent	absent	NA
31	M	40	motor weakness	present	lt frontal	Lateral bra	3	High	positive	loss of ex	positive	8%	positive	negative	Astrocyto	High	high	Moderate	absent	absent	NA
32	F	30	visual disturbance	present	lt frontal	Lateral bra	2	Low	positive	loss of ex	positive	3%	negative	negative	Astrocyto	moderate	high	Moderate	absent	absent	NA
33	M	30	headache	absent	Corpus cal	Midline	3	High	positive	retained r	negative	10%	negative	negative	Astrocyto	moderate	high	Moderate	absent	absent	NA
34	M	17	seizures	present	lt tempor	Lateral bra	1	Low	negative	Retained	positive	1%	positive	negative	Pilocytic a	low	low	mild	absent	absent	NA
35	M	35	seizures	present	rt tempor	Lateral bra	2	Low	positive	loss of ex	positive	4-5%	negative	negative	Astrocyto	High	low	Moderate	absent	absent	NA
36	M	54	headache	absent	rt tempor	Lateral bra	4	High	negative	retained r	negative	18-20%	positive	positive	Glioblastc	High	high	high	present	present	tumor progression
37	F	12	headache	absent	rt tempor	Lateral bra	1	Low	negative	retained r	negative	2-5%	positive	positive	Gangliogli	low	low	high	present	present	NA
38	M	14	seizures	present	septum pe	Midline	1	Low	positive	loss of ex	positive	1%	positive	negative	Low grade	moderate	low	mild	absent	absent	NA
39	F	43	seizures	absent	rt tempor	Lateral bra	4	High	negative	retained r	positive	10-12%	positive	negative	Glioblastc	High	high	Moderate	present	present	NA
40	M	52	headache	present	rt parietal	Lateral bra	4	High	negative	retained r	positive	20%	negative	negative	Glioblastc	High	high	Moderate	present	present	tumor progression

gross total excision	yes	yes	12months	40	3	10	4	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	no
gross total excision	yes	yes	15months	60	2	20	4	yes	no	yes	yes	no	no	yes	no	yes	yes	no
gross total excision	no	no	1month	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
gross total excision	yes	yes	NA	80	1	60	2	yes	yes	yes	no	no	no	yes	yes	no	yes	no
gross total excision	yes	yes	16months	90	0	80	1	no	yes	no	no	yes	no	no	no	no	yes	no
subtotal resection o	no	no	NA	100	0	100	0	no	yes	no	no	no	no	no	no	no	no	no
gross total excision	no	no	2months	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
gross total excision	no	no	NA	100	0	100	0	no	no	no	no	no	no	no	no	no	no	no
gross total excision	yes	yes	NA	100	0	100	0	no	no	no	no	no	no	no	no	no	no	no
gross total excision	yes	yes	NA	100	0	100	0	no	no	no	no	no	no	no	no	no	no	no
gross total excision	yes	yes	NA	80	1	80	1	yes	no	no	no	yes	no	no	no	no	yes	no
gross total excision	no	no	NA	100	0	80	1	no	yes	no	no	no	no	yes	no	no	yes	no
gross total excision	yes	yes	NA	80	1	80	1	yes	no	no	no	yes	no	yes	no	no	no	no
gross total excision	no	no	NA	80	1	60	2	no	no	yes	no	no	no	no	no	no	yes	yes
gross total excision	no	no	NA	100	0	100	0	no	no	no	no	no	no	no	no	no	no	no
gross total excision	yes	no	5.5months	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
gross total excision	no	no	NA	100	0	100	0	no	no	no	no	no	no	no	no	no	no	no
gross total excision	no	no	NA	100	0	100	0	no	no	no	no	no	no	no	no	no	no	no
gross total excision	yes	yes	NA	80	1	80	1	yes	no	yes	no	yes	no	no	no	no	yes	no
gross total excision	yes	yes	14months	60	2	20	4	yes	no	yes	yes	yes	no	yes	yes	yes	yes	yes

23	seizures	present	lt tempora	Lateral bra	2	Low	positive	loss of ex	positive	3%	positive	negative	Astrocyto	High	low	mild	absent	absent	NA
22	visual disturbance	present	rt frontal	Lateral bra	4	High	positive	retained r	positive	18-20%	positive	negative	Glioblastc	High	high	Moderate	present	present	NA
51	motor weakness	present	lt frontal	Lateral bra	3	High	positive	retained r	negative	18-20%	negative	negative	Oligodenc	moderate	high	Moderate	absent	absent	NA
42	seizures	present	rt frontal	Lateral bra	4	High	negative	retained r	negative	20%	negative	negative	Glioblastc	High	high	Moderate	present	present	tumor progression
32	headache	absent	rt frontal	Lateral bra	3	High	positive	retained r	negative	8-10%	negative	negative	Oligodenc	moderate	low	Moderate	absent	absent	NA
35	seizures	present	rt insular	Lateral bra	2	High	negative	loss of ex	negative	1-2%	positive	negative	Astrocyto	low	low	mild	absent	absent	NA
36	seizures	absent	rt frontote	Lateral bra	2	Low	positive	retained r	negative	6%	positive	negative	Oligodenc	low	low	mild	absent	absent	NA
43	visual disturbance	present	rt frontop	Lateral bra	4	High	negative	retained r	negative	18-20%	negative	negative	Glioblastc	moderate	high	Moderate	present	present	NA
45	seizures	absent	rt frontote	Lateral bra	2	Low	positive	retained r	negative	1-2%	positive	negative	Oligodenr	moderate	low	Moderate	absent	absent	NA
52	visual disturbance	present	lt frontote	Lateral bra	4	High	negative	retained r	negative	18%	negative	positive	Glioblastc	moderate	high	high	present	present	NA
26	headache	absent	lt parietoc	Lateral bra	2	High	negative	retained r	negative	2-3%	negative	positive	Ependym	low	low	high	absent	present	NA
49	seizures	present	rt frontal	Lateral bra	4	High	negative	retained r	negative	1-2%	negative	negative	Glioblastc	High	high	high	present	present	NA
39	motor weakness	present	lt thalami	Thalamic	4	High	negative	retained r	positive	6%	negative	positive	Diffuse as	High	sparse	high	present	present	NA
39	motor weakness	present	lt thalami	Thalamic	4	High	negative	retained r	positive	40%	negative	negative	Diffuse as	High	high	high	present	present	tumor progression
24	headache	absent	lt parietal	Lateral bra	2	High	negative	retained r	negative	7%	negative	negative	Diffuse ac	moderate	low	Moderate	absent	present	NA
26	motor weakness	present	lt frontal	Lateral bra	3	High	negative	retained r	positive	8-10%	negative	negative	Diffuse ac	High	high	Moderate	present	present	NA
55	seizures	present	rt frontote	Lateral bra	4	High	negative	retained r	negative	2-3%	negative	negative	Glioblastc	High	high	high	present	present	tumor progression
52	headache	absent	lt frontal	Lateral bra	4	High	negative	retained r	negative	2-3%	positive	negative	Glioblastc	High	high	Moderate	present	present	tumor progression
28	visual disturbance	present	rt frontal	Lateral bra	2	High	negative	retained r	positive	6-7%	negative	negative	Oligodenc	moderate	low	Moderate	absent	absent	NA
37	seizures	absent	rt frontal	Lateral bra	3	High	negative	retained r	negative	5%	positive	negative	Oligodenc	moderate	low	Moderate	absent	absent	NA

gross total excision	yes	no	NA	100	0	100	0	no	no	no	no	no	no	no	no	no	no	no	no
gross total excision	yes	yes	yes	80	1	60	2	yes	yes	yes	no	no	no	yes	no	no	yes	no	
gross total excision	yes	yes	NA	90	1	90	1	no	no	no	no	no	no	no	no	no	yes	no	
gross total excision	no	no	4months	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
gross total excision	yes	yes	NA	90	1	90	1	yes	no	yes	no	no	no	no	no	no	yes	no	
gross total excision	yes	no	NA	80	1	80	1	no	no	yes	no	no	no	no	no	yes	yes	no	
gross total excision	yes	yes	NA	100	0	100	0	no	no	no	no	no	no	no	no	no	no	no	
gross total excision	yes	yes	NA	100	1	100	1	no	no	no	no	no	no	no	no	no	yes	no	
gross total excision	no	no	NA	70	2	60	2	no	no	yes	yes	no	no	no	no	no	yes	yes	
gross total excision	yes	yes	NA	80	1	60	2	yes	yes	yes	yes	no	no	yes	no	yes	yes	yes	
gross total excision	yes	no	NA	100	1	100	1	no	no	no	no	no	no	no	no	no	yes	no	
gross total excision	yes	yes	NA	100	1	100	1	no	no	no	no	no	no	no	no	no	yes	no	
subtotal resection of	yes	no	NA	90	1	90	1	no	no	yes	yes	no	no	no	no	yes	yes	no	
subtotal resection of	yes	yes	9months	40	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
gross total resection	no	no	NA	90	1	90	1	yes	no	no	no	no	yes	no	no	no	yes	no	
gross total resection	yes	no	NA	100	1	100	1	no	no	yes	no	no	no	no	no	no	no	no	
gross total excision	yes	no	7months	40	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
gross total excision	yes	yes	9months	20	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
gross total excision	yes	no	NA	100	1	100	1	no	no	no	no	no	no	no	no	yes	yes	yes	
gross total excision	yes	yes	NA	100	1	90	1	no	no	no	no	no	yes	no	no	no	yes	no	